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“Buy Right”

As an HMA representative to the Chamber of Commerce of Hawaii Health Care Reform Task Force, I was invited to attend a breakfast on 25 September at the Pacific Club hosted by Blake Waterhouse MD of Straub Clinic & Hospital, to hear Walter McClure PhD speak on the topic of “Buy Right”.

McClure is the chair of the Center for Policy Studies, a Minneapolis-based think tank. He was a featured speaker at the preceding day’s conference at the East-West Center on “Outcomes Measurement: Assessing Quality of Health Care in Hawaii”, initiated by the Pacific Health Research Institute and co-sponsored by the HMA and other organizations.

Dr McClure was a dynamic speaker who held an audience of some 40 leaders of our community enthralled with his presentation, well past the time when many had to leave to go to work.

I was pleased to see that the breakfast buffet was austere, commensurate with the economic recession that has struck Hawaii belatedly in relation to the event on the Mainland—mixed fresh fruit and goodies from the bakery. It was healthful!

My notes include the following:

McClure: Purchasers of health care will ask you: “Who is the better [provider] and for less [money]? We’ll send patients to you.” This struck me aghast. Was he about to give us a dissertation about sending sheep to the shearers?

Then I was reassured when he gave us the dictum that what the consumer needs is quality [in medical care, as in all transactions]. But once again, he came across with a wicked curveball pitch: “MDs tend to skew services in order to make more money.” I simply could not accept that.

McClure went on to compare buying health care as one would buy a car; ie a packaged product with an expected cost for a certain value. Incredible, I thought! Purchasers/consumers can expect specific performance and outcome when buying a new car; if they happen to pick a lemon, there are ways to stop payment until satisfaction is obtained: Corrective repairs or a new car. It is not so when a cholecystectomy is in the offing; there is no guarantee whatever that the outcome will be perfect, that no complications will occur, that the patient is expected to be quite healthy and fit pre-op, etc *ad infinitum*! He cited the rather outstanding fact (not what some of my patients have reported to me) that the Mayo Clinic “does it 20% cheaper and is in the 1% of top quality providers.”

His bottom line was in fine print, visible under the microscope of business economics: “Cost per beneficiary is the criterion in business.”

However, with one thing he said I could agree: Physicians could and should be more efficient in terms of health care, ie preventive medical care, by utilizing the many paramedical per-

sonnel, including nurse practitioners and social workers, to reach out into the community to bring in the prenatal patients earlier, to find the sick and bring them in for care *before* the ill or injured patient needs hospitalization. Primary care centers such as Kokua Kalihi Valley do that, I know; the Maluhia Project has demonstrated a large saving in reduced emergency room visits by the elderly, infirm, near poor. However, public expenditures and costs are still large.

Is it the physician’s role to be a social worker as well? Must he or she increase his or her overhead by hiring a social worker? And, what of the patient’s responsibility to look after and preserve his or her own good health?

Dr McClure cited the city of Cleveland as now having 17% of its major purchasers of health care, presumably insurance carriers and large businesses, in the “Buy Right” program, whereby they have persuaded [maybe arm-twisted?] patients to see providers of medical care who “provide better for less”.

Having a sense of the American people as being very individualistic and choosy, I figure that percentage will not rise significantly. Can you imagine persuading or pushing the people of Waianae to attend only a set group of physicians located in Wahiawa for their health needs? McClure belittles the “services” physicians provide, as mentioned at the beginning of this report; he seems not to understand that the laying-on of hands by the physician, instead of another CAT-scan, is often all the care some patients need.

However, there is some validity in McClure’s ultimate goal: That if the “better for less” concept were to spread to all providers in our community, the standards of medical care would be raised overall. We physicians should make that our goal and shortcut the process to that end, so that there will be no reason to “shift” patients, like herding sheep.

McClure’s tenets are based on the “sound market” economic principle espoused by Adam Smith in the 18th century.

Readers who wish to delve further into this “Buy Right” concept should go to the source—Dr McClure’s speeches and written articles.

J I Frederick Reppun MD
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Health care and more health care

Fred Gilbert Jr, who has been in Hawaii long enough to see the evolution of medical care from plantation medicine of 50 years ago to the present system of preponderantly fee-for-service, high specialization, high-tech and very costly care of disease, is certainly imbued with the facts of the change. Readers will find Fred's article in this issue of the *Journal*, in which he dubs the current practice of medicine as being "upside down, inside out and going backward," interesting and rather provocative.

We take issue with Fred on several scores, but honor him nevertheless for his advocacy role on behalf of his patients, as a warm and caring physician.

To go back in time to the days of plantation medicine: It was good in the sense that good doctors were good in dispensing it, albeit under the watchful, moneyed eye of the plantation manager. The patients were given basic, adequate care as a part of management's paternalistic attitude: A sick or injured worker was a liability with an adverse impact on profits (the bottom line). High-tech medicine was unheard of (its absence good for profits, too!).

The plantation physician was a "gatekeeper", a job that was made easier by the difficulties of interisland transportation and sometimes intransigent lack of transportation, facilities and specialist services.

Fred seems also to have forgotten how it was to practice in the military; that was a capitation system of medical care somewhat less paternalistic than was plantation medicine. Under both systems of medical care, the physician had to be innately professional and dedicated to the best interests of his or her patient—despite the sometimes powerful tendency to put his or her feet up on the desk and order an aspirin or an enema sight unseen. It is a credit to the profession that physicians were mostly not of that ilk. The same can be said of the physicians in the Kaiser Permanente plan—they are dedicated and good.

The Kaiser Plan is the prototype for the burgeoning HMOs in this country, but the latter feature fee-for-service for the most part. They are federal government—encouraged. This pushes patients in that direction, as do employers and insurance carriers. Despite disclaimers to the contrary, "quality" is subservient to "cost control," the latter being the primary focus of all 3—government, employers and insurance companies. The general public goes along because individuals know that *all doctors* who are licensed to practice are supposed to be *equally* well-trained and capable; so what difference does it make which doctor is on call?

However, many Americans are highly knowledgeable about things medical and are sometimes rather insistent on choosing a personal preference.

Fred's use of the term generalists is a bit disturbing. We think he equates it with "primary care physicians", but there is a distinction. The latter are now presumed to include generalists (few remain of this older generation of doctors), family physicians (now specialists, too), internists and pediatricians. The latter 2 categories are presumed to do no surgery and deliver no babies. Obstetricians are now being considered as primary care physicians; they are, in the sense of taking care of women patients even in advance of pregnancy. Internists, pediatricians and obstetricians are actually specialists, but so is a family physician who does no surgery and does not deliver babies.

Finally, we think that Fred's "new" generalist will be totally overburdened if he or she must also be the community's social worker, sanitation officer, police officer, drug-enforcer, and even a planner. Fred seems to argue for managed care to the max. Granted that the primary care physician—a better term is the PMD, private medical doctor (no matter what kind of primary medical care), needs to be thoroughly aware of the many vicissitudes of modern living affecting his or her patient in the family and in the larger community. We feel that health is a matter of personal responsibility and a part of that should be the person's choice of a physician and the personal, private contract with him or her to be the patient's advocate. The Oath of Hippocrates requires the physician to do his or her utmost to heal the patient; this implies no interference by a higher authority such as government, employer or insurance payer. The Oath does not stipulate that the physician must "keep" his or her patient healthy, and it is not in the contract between the 2.

The modern physician is burdened enough without making him or her a social worker or babysitter. It's not the PMD's job to enforce no smoking, no alcohol, no fat or fast foods and thrice-weekly strenuous exercise, much less to see the patient doesn't beat his wife or kids. To persuade, to educate, to manage the patient's difficult choices and decisions in the course of being referred to specialists, yes! But to "manage" in the sense of mandate, a loud no!

We two Freds would relish a discussion on the part of our readers of "turning medicine upside down, inside out" and reversing course.

J I Frederick Reppun MD
Editor

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Health care in the United States: The need for a new paradigm

Fred I Gilbert Jr MD*

American medicine, as practiced at the close of the 20th century, has some major problems that we categorize as being "upside down, inside out and backward". Fortunately, these are correctable.

First, it is upside down. Primary care should be the foundation of the structure upon which the entire practice of medicine is built. However, it is not working that way. Specialists and subspecialists have become the wobbly foundation of health care in America. This makes our care system "upside down", with the underpinning being procedure-oriented specialists who get only a glimpse of whole patients and their needs.

That is not the only problem. The system is also "inside out". The key person in the entire system, and the whole reason for health care, is the patient. The patient has become lost within a very complex, disconnected system. The welfare of the patient should be the core that provides the energy that drives the system. Does it really work that way? Not quite. The patient, not necessarily his or her welfare, sometimes becomes the grist for the medical mill. The system is turned inside out.

And it is "backward". But how can we believe the American health care system, which has made such enormous strides in the last century, can be called backward? There is no argument regarding the high peaks of achievement in both research and practice; but there are deep valleys with a persistent and increasing percentage of the U.S. population (with the exception of Hawaii) that has no health insurance coverage. In addition to 30-million people without health insurance, there is a worsening of many of our vital statistics. Infant mortality is increasing as is mortality from many preventable diseases such as lung cancer. Patients, their physicians, the government and insurance carriers are all dissatisfied with our system. Are we moving forward or backward? The figures indicate that in many areas we are slipping backward.

How it was before WWII

Prior to World War II, 1941 to 1945, most physicians were engaged in Fee-for-service, private, general practice. With few exceptions, both patients and physicians were satisfied with their care. Physicians and patients negotiated a fee for whatever service was required—usually satisfactory to both. There was also an unwritten contract between the two and a written oath binding the physician. The unwritten contract was that the physician would do everything within his or her power to improve the health of the patient, and the patient agreed to do everything within his or her capability to cooperate in achieving the desired outcome. The written oath, of course, was The Oath of Hippocrates.

Medical students were introduced to medicine as being a sacred trust and were required to take the oath at a rather solemn ceremony. For more than 2,000 years this has been the code of ethics in the practice of medicine. The welfare of the patient was deemed to be of paramount importance and the patient was not to

be exploited in any manner.

In the late 1930s the nation was just emerging from the Great Depression. Almost no one was wealthy and the cost of everything, including medical care, was of considerable concern. It was expected that every physician would spend at least a part of the day in the hospital or a full afternoon every week in the outpatient clinic caring for welfare patients termed the medically indigent. These patients were generally cared for in hospitals affiliated with university schools of medicine. In general, their care was excellent but the patients were denied what the rest of society had—the free choice of physicians.

Health insurance plans

There was increasing concern, even among the employed, that a catastrophic illness could wipe out a family's financial resources. To circumvent an individual or family being so devastated by illness, Blue Shield/Blue Cross Insurance plans made their appearance. In Hawaii, the HMSA insurance plan appeared shortly before WWII as a result of cooperative efforts by school teachers, social workers and physicians. Physicians had no great objection to this arrangement because they would still be paid pre-determined, adequate compensation for specific services.

On the surface this seemed to be a good arrangement. Cost of medical care was distributed over groups of people and periods of time. There were, however, persisting major disadvantages to this arrangement. First of all, it handsomely rewarded physicians for doing "something" to the patient whether or not the "something", in the form of a test or operation, made any difference in the ultimate outcome. This was accepted and easy to rationalize because an x-ray of the chest or removal of a gallbladder could be documented and priced.

In contrast, however, it was very difficult to document and to put a price tag on a physician's conviction that a patient did not need an x-ray or cholecystectomy. It is virtually impossible to arrive at a fee schedule for successfully getting a patient to stop smoking and thus avoiding not only cancer of the lung, the most common fatal cancer of both sexes, but possibly eliminating over \$100,000 worth of surgery, countless costly diagnostic procedures, chemotherapy, prolonged hospitalization and premature death.

The introduction of medical insurance also had the drawback of moving the patient out of the decision-making loop once he or she had decided on the specific insurance carrier and type of policy. The unwritten contract between patient and physician now includes a third party and a written contract with the insurance carrier that binds both physician and patient, as well as hospitals. Need it be added that there has been a continuing difference of opinion between hospitals, physicians as suppliers of services, and insurance payers for services, as to what is a proper financial arrangement? If the insurance carrier agrees to the fee increases for suppliers of services, it is reflected as an increase in the next year's insurance premium paid by patients or their employers. If the

*Pacific Health Research Institute, Honolulu, Hawaii
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(Continued on page 10) ►

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carrier doesn't agree to an increase, the battle goes on. The insurance system does not cover the uninsurable, nor does it cover preventive services.

The capitation plan

As the United States entered into WWII, a red-haired young physician who had previously worked with industrialist Henry Kaiser by furnishing medical care to his construction workers was asked to develop a plan for Kaiser workers who were building liberty ships in Richmond, California. Sidney Garfield MD agreed to develop the Kaiser-Permanente Health Plan that blended a not-for-profit health plan, including hospital and outpatient facilities, with a for-profit group of physicians. Medical care was paid for by capitation rather than on the Fee-for-service basis (from the Latin *capit* or head tax). The difference was that providers of care were paid per enrolled individual regardless of the presence or absence of sickness, diagnostic tests performed, or operations undertaken. All in all this has worked well, largely because of the organizational genius, professional competency and pioneering efforts of the founding half-dozen physicians, including Sidney Garfield, Morris Collen, Cecil Cutting (the brother of the first dean of the UH School of Medicine) and several others. It is, in our opinion, an improvement over the Fee-for-service system in that it has the potential for encouraging efforts and rewards for promoting and maintaining good health, as well as preventing disease, which is as yet only partially realized otherwise.

Adding to the pool of players in the U.S. health care system—patients, providers and payers—in 1965, the Federal Government entered as an important player by introducing Medicare and Medicaid, designed to care for the elderly and the poor respectively by funds obtained through taxes.

The biomedical model

During this same time frame, when efforts were being made to distribute the cost and availability of health care more equitably, an unprecedented surge of achievement in basic biology and medicine took place. Within this bio-medical framework, hearts were being transplanted, damaged joints replaced, previously fatal diseases including certain types of cancers were being cured or controlled. Smallpox was eliminated and poliomyelitis became preventable. Genes that determine who we are, how we function, and to a great degree the diseases that we may get are being decoded, spliced and replaced. Paralleling this biomedical research and health care achievement, medical care became centered on specific organs, disease, and technical interventions. General practice, oriented to care for the whole patient, gave way to specialist care designed to care for diseased organs. Although history may recognize the last half of the 20th century as the Golden Era of Medicine, if this be true, not many people are overly happy about it.

Discontent

Almost half of all physicians over age 40 or who have been in the practice of medicine for at least a decade state they would not choose medicine as a career if they had to make the decision again. This incidentally is in contrast to what attorneys state: Only 15% would pick a career other than law (we suspect there may be a relationship between attorneys' contentment and physicians' dis-

content!).

Businesses, both large and small, are unhappy, particularly about the cost of medical benefits for their employees and recently have expressed concern that the quality doesn't match the cost. Large companies, such as the automotive industry, indicate part of their problem in competing with foreign automakers is the cost of medical care in the U.S. Smaller companies, which sometimes employ many more workers than do the large ones, are strongly protesting the shift in policies that require them not only to pay for the medical care of their employees but also to pay someone to look after the increasing government paperwork that is required.

Hospitals have become extremely unhappy about the decreasing level of reimbursements, often unpaid-for services, and greater competition. There has occurred a resultant bankruptcy of a large number of American hospitals over the past few years. Insurance carriers are unhappy at being constantly caught in the squeeze between enrollees who on one hand expect the best and most expensive care possible as long as someone else pays for it and on the other hand become very upset as premiums increase.

Most important of all, patients are not happy with their health care. They may be satisfied with their personal physician but not with the overall system. Many have been led to believe that good health can be bought. The message has been: "Don't worry too much about what or how much you smoke, eat or drink; if the arteries of the heart get clogged or the lung cells turn to cancer, treatment is available". It is much more financially rewarding for all members of the supply-side of care to diagnose and treat the results of unhealthy life-styles than to spend the time and effort to assist in the development of more healthy life-styles or to modify unhealthy life-styles beneficially.

The federal government, composed of those trusted public servants who congregate in Washington, flush with victories in improving education, reducing drug-related problems, assisting in providing housing for the homeless and regulating savings and loan agencies, has seized the opportunity to turn public concern into a matter of personal job security. As with many of government's well-meaning efforts, nationalization of health care will contribute more to the problem than to the solution. The federal government has, through its control of Medicare and Medicaid funds, become a major force in preventing needed innovations in health care. The government achieves this through rigid guidelines and regulation, requiring massive paperwork. Jack Lewin MD, the director of the Hawaii Department of Health, who has spearheaded much of Hawaii's efforts to provide all residents with health care, can attest to this—as can every practicing physician in the nation. Paradoxically, the same national politicians who created these restrictive laws and regulations are the most strident voices calling for health care reform and national health insurance. None has suggested the proper, needed changes in design and structure.

If everyone involved is unhappy with the health care system, chances are there is a problem. There is no denying the problem is a complex mix of poor distribution of care, with millions of Americans uninsured, and cost of care running about 12% of the GNP; this is in contrast to that of Canada and other emerged nations where it is in the neighborhood of 8%. This year members of the U.S. Congress held public meetings throughout the country to hear the people voice their concerns about health care that is largely focused on which of 5 plans for national health insurance they

(Continued on page 12) ►

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preferred—all of which have as a major goal the control of costs rather than restructuring the system.

Faulty assumptions

To no one's great surprise, many people suggested cost was the problem and national health insurance the cure. In Hawaii, Governor Waihee appointed a blue-ribbon panel on health care in 1991 to address the problem of the high cost of health care in Hawaii. A report was to have been made in January 1992 and was recently released.

Most efforts to improve the ailing health care system are based on 3 assumptions—all wrong:

- 1) The cost of health care is the cause of the problems;
- 2) redistributing the cost and the remuneration for giving care will provide the leverage to bring about needed reforms and result in more equitable care;
- 3) medical and political policy experts have the knowledge and wisdom to solve the personal health problem of individuals.

Consequence, or cause?

The increase in cost of medical care is the result of a badly designed and poorly constructed system. The latter's poor design and function includes inappropriate and wasteful use of resources, excessive government bureaucracy and needless procedures done to prevent or reduce outlandish malpractice awards. It also costs too much because of stifling barriers to creating solutions. Since it became apparent that Medicare and Medicaid were costing far more than anyone anticipated and actually are contributing to the high cost of health care, there has been an almost unending tinkering with the financial aspects of care, usually masquerading as an effort to improve quality.

Redistributing the financial rewards for providers of care has not solved this complex puzzle. Diagnosis-Related Groups (DRGs) and Resource-Based Relative Value Scale (RBRVS) are the most recent federal attempts to solve the health care problem by financial tinkering.

The DRGs provide a means of payment to hospitals on the basis of predetermined dollars according to the diagnosis. The theory is that excessive hospital costs will be reduced by limiting the days the patient stays in the hospital and curtailing unnecessary tests and procedures.

The RBRVS pays for physician services based on years spent in training, the complexity of the medical problem and the degree of skill required in its resolution. These are massive programs covering all Medicare and Medicaid patients and will probably be expanded to cover all privately insured patients. They will neither provide for, encourage, nor even permit the necessary restructuring of care (both DRGs and RBRVS will eventually fail).

Insurance plans have flattened out the economic peaks and valleys in health care, which is desirable. The Kaiser-Permanente capitation plan has the proper foundation to build the structure in which there are greater rewards—financial and other—in keeping patients healthy. This includes keeping them out of doctors' offices and hospitals, with the opportunity to enjoy a happy functioning family, productive work and the realization that they are helping to preserve a peaceful, desirable environment for future generations. This hasn't happened yet in Kaiser-Permanente or any other health care plan, partly because doctors and nurses

have jumped through the same hoops in their professional training as their cohorts practicing in other settings. They are operating within the confines of the same biomedical paradigm as the rest of us and are kept exceedingly busy—caring for the health problems as defined within this paradigm.

The third incorrect assumption is probably the most to be feared of all 3. No expert is knowledgeable enough or wise enough to make decisions for the health and welfare of another, adequately informed, rational adult, and many children. Every person has the right and responsibility to make his or her own decision about personal health.

All of the foregoing indicate that past, present, and most future plans for improving health care have not and will not work within a care system largely limited to the specialist, Fee-for-service, biomedical model. It may be that we need to look at a different way of conducting health care.

Responsibility

Both individuals and communities must become more involved in their health. First of all, those who are to be cared for within the system must be encouraged and permitted to define their individual as well as collective needs. An informed individual is in the best position to make decisions regarding his or her well-being. Only recently has it been recognized and accepted that personal life-style has considerable influence on an individual's health. We were very slow to appreciate that substance abuse in the form of calories, alcohol, drugs, tobacco, and physical inactivity account for most premature morbidity and mortality.

We are only beginning to think about a community's responsibility for its own health. We have scarcely started to address community diseases of multifactorial causes. These diseases involve members of the community who are homeless, jobless, poorly educated, mentally dysfunctional, poorly nourished, financially poor and without hope; they are frustrated and angry. It also includes those who exhibit irrational, destructive violence. If health care has a goal of reducing morbidity and mortality, it must recognize the foregoing as health issues. The most common cause of death in young black men is a "disease" caused by a gun or knife. Communities must become involved in diagnosing and treating health problems as defined by the community itself. This mechanism whereby a community defines its collective needs and individuals define their individual needs must be a dynamic process to address properly the constantly changing needs in an equally constantly changing health care environment. Both individuals and communities have the shared responsibility of differentiating appropriate needs from inappropriate desires and matching needs to finite health care resources.

A new type of physician, a generalist in contrast to a specialist, must be created to practice medicine in a vastly different way from his or her predecessors. He or she must perceive individuals and the collection of individuals who make up a community as his or her responsibility in a different manner. This physician must also acquire the tools and methods to meet this responsibility. This does not mean a break with the traditional values of medicine as a sacred trust, which puts paramount value on promoting the well-being of the patient. It does mean that to serve individuals and communities adequately as a generalist, scientific knowledge and art applicable to resolving community health problems as well as

individual health problems must be used. These include the tools of epidemiology, biostatistics, informatics, decision analysis, outcomes research, economics, social psychology, cultural anthropology and demography. Awareness of the social, environmental and psychological influences on health care, combined with the new tools described, will contribute to the creation of a more rational model of health care.

The biomedical model has been the framework for outstanding advances in medicine over the past century. We are not advocating that it be abandoned. Neither are we advocating that specialist care be abandoned. However, our model must include the social, environmental and psychological factors that play a much more important role on health than previously appreciated—a biomedical-psychosocial model. This generalist physician functioning within this model will require an intellectual foundation involving all social and scientific disciplines. Colleges of health sciences, and particularly schools of medicine, must revamp their curricula and move more of their teaching out of academic ivory towers and hospitals and into community health centers and other community facilities. When a change of this magnitude is made, all elements of the system must change. This includes everything from changing responsibilities of physicians, nurses, health aides, technicians and administrators. It also will require change in fiscal arrangements, facility design, data management, research and teaching activities, to name a few.

The contrast

We propose contrasting the generalist—a community-oriented, capitation-paid, biomedical/psychosocial-model physician—to the specialist—the hospital-oriented, Fee-for-service, biomedical model. In this new model of health care, the generalist will play a key role. The present generalist is underrepresented (30% of the total number of physicians in the U.S.), overworked, and for the greater part, underpaid. In Hawaii we do better, with 52% of physicians being generalists. Fifty-one percent of medical students graduating from the UH John A Burns School of Medicine in the past 3 years—1990, 1991 and 1992—have selected residency training that will prepare them as generalists. Nationwide the percentage will have to almost double over the next decade, with a corresponding reduction in specialists. Specialists must remain in the system but must be utilized more appropriately.

Emphasis on locus of care must shift increasingly from hospital-oriented care to community-oriented health centers. The method of paying for health care also needs to shift from the Fee-for-service system that thrives on sickness, costly procedures, overspecialization and neglect of preventive efforts to a capitation system that has more positive incentives to keep people healthy with more judicious use of costly high-tech interventions.

The biomedical model presently utilized in medical teaching, research and services is not to be abandoned but must be modified and broadened to include the broader social, economic and other factors that influence health and disease. The present model needs to be expanded into the biomedical/psychosocial model.

Physicians, nurses, allied health personnel and others would have newly defined jobs with increased emphasis on preventive care and health promotion. Computerized medical records would provide the data bases needed for both individual and community health risks and problems. The data generated would also provide

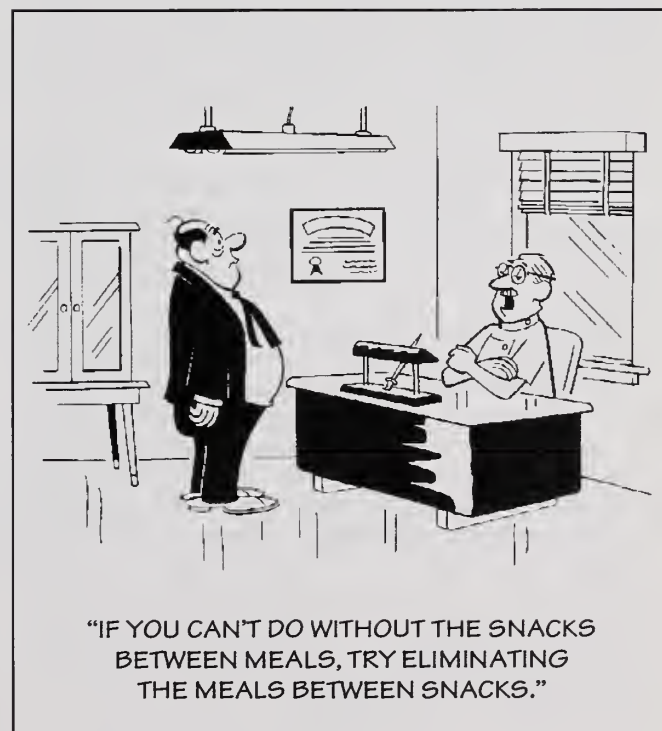
the capability to determine the relationships between decisions made, actions taken, and eventual outcomes. Decision analyses and outcomes research centering on cost and effectiveness of various types of interventions and noninterventions would provide more accurate information available to physicians, patients and communities to benefit their collaborative efforts regarding health. Decisions made and actions taken would be driven by hard data, most of which is lacking within our present care system. Students in medicine, nursing, public health and social work would share learning experiences gleaned from dealing with health problems and their solutions from a new perspective within a different paradigm.

Hawaii has had considerable success with some elements of the health system that we have just described. The plantation health care system was a community-oriented capitation system staffed by generalists. It was by far the best rural health care system that existed in its time. The lessons learned from the plantation system continue to influence health care in Hawaii.

Hawaii has a legitimate right to be called *The Health State*. Its citizens live longer and have fewer preventable deaths than any other state in the U.S.

Almost all of its people are covered by health insurance. The cost of health care is probably the lowest in the nation, consuming only 8% of its "GNP" as compared to the rest of the nation's 12%.

With continued improvement in health care in Hawaii, the system can be made right side up, inside in and moving forward. The rest of the United States might well profit from our experience.



Breast-feeding versus formula: Cost comparison

Lydia A Jarosz PhD*

Peterkin and Walker published in 1976 a cost estimate of feeding a baby in the U.S.¹ At that time, they found there was little difference in cost between breast-feeding and formula feeding. Since then, however, the cost of formula has risen drastically—more than 150% during the 1980s². One researcher estimated that food and feeding equipment cost \$855 in the first year³. Whereas the cost of formula is quite apparent when a family buys it, the cost of breast-feeding is hidden.

Introduction

The cost of feeding a newborn is of interest to both the family and the State of Hawaii for planning purposes. There are over 19,000 births annually in the State⁴; a large number of families make decisions on how to feed infants each year. Of the surveyed women residing on Oahu who had delivered in 1983 or 1984, 58% breast-fed their infants exclusively at the time of hospital discharge⁵. Another 19% of the infants were bottle-fed exclusively (presumably with infant formula), whereas 24% were fed breast plus bottle. Preliminary results from an update of this study showed that of all the newborns in Hawaii, at the time of discharge from the hospital, 50% were breast-fed, 22% were formula-fed and 28% were fed both by breast and with formula^{5,6}.

Although the changes from 1984 to 1990 in feeding methods are not dramatic, if there is an obvious difference in cost between feeding methods, that observation could affect a family's selection of feeding method and could represent a significant difference in the absolute cost of feeding infants in Hawaii.

Our article presents estimates of current costs associated with 62 days (2 calendar months) of either exclusive breast-feeding or formula-feeding of a hypothetical healthy, full-term newborn in Honolulu. It does not address other important issues regarding the feeding of newborns; for example, compositional differences between these 2 foods (including non-nutritive differences such as immunoglobins and growth factors), how the infant is fed and other aspects of maternal-

infant bonding. Reviews of biological aspects of human milk and infant feeding are available^{7,8}. Neither is the equipment used for feeding considered, since it varies widely depending upon individual needs and preferences.

Throughout this article, the term milk refers to either human breast milk or infant formula.

Methods

The cost of infant formula and the cost of food a mother would consume to produce milk were calculated for the first 62 days of an infant's life. A 62-day period was selected to allow for cost comparison. Costs were assessed based on several assumptions as described below.

Based on the infant

(1) To simplify calculations with respect to the amount of milk needed by the infant, the full-term, healthy infant was assumed to weigh 4.3 kg for the first 31 days of life and 5.2 kg for the second 31 days of life. These are the 51.3 and 50.3 percentile weights (Z scores of +0.03 and +0.01 and 100.6 and 100.1% of the median, respectively) at 1 and 2 months of age respectively, for a male infant as assessed, using the Centers for Disease Control anthropometric software (1988). By using the weight at the end of the period rather than that at the beginning, cost estimates were slightly higher than actual costs, but the relativity would be the same.

(2) Cost calculations were based on the assumption that dietary energy needs were the same in both formula and breast-fed infants and were 108 kcal per kilogram of body weight per day. According to the National Academy of Sciences⁹, this is about 15% higher than "recent estimates". However, a study published since the NAS document came out suggests that this estimate may be quite correct for 1-month-old formula-fed infants, but it might overestimate the needs of breast-fed infants of the same age, because they had an average need of 99 kcal/kg/d; however, the difference in energy needs was not statistically significant¹⁰.

There are additional and substantial data which suggest that breast-fed infants utilize energy more efficiently, including its better nutrients, as compared to infants fed proprietary milks^{9,11}. However, since it is not yet clear whether the differences are statistically significant or not, the same energy values were applied to both foods. Thus, the cost calculations probably represent an overestimate of cost as applied to breast-feeding.

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Based on the mother

(1) The mother was assumed to be the hypothetical woman described by the NAS for the purpose of discussing the recommended dietary allowances⁹; ie she was between 25 and 50 years of age, weighed 63 kg (138 lbs), was 163 cm (64 inches) tall, and needed an average amount of energy per day to meet her own needs (36 kcal/kg or 2268 kcal). These assumptions do not have a direct impact on the calculations of the cost of breast-feeding but are mentioned as points of reference. There are 2 assumptions that do affect calculations: the mother produced milk with an energy content of 70 kcal/100 ml and her efficiency in converting dietary energy into human milk energy was 80%, resulting in a need of about 85 kcal of dietary energy to produce 100 ml of human milk⁹. This translates into an intake of an energy need 21% above that needed by the infant.

Based on the foods

(1) The energy content of proprietary milk as fed to the infant was 65 kcal/100 ml (20 kcal/oz).

(2) In preparing formulas to feed to the infant: (a) Concentrates required equal volumes of water and formula; and (b) powders required that water be added in preparation to the grams of powder, as stated on the product label, in order to prepare a specified amount of formula. The amount of powdered formula needed to mix with 2 ounces of water varied from 8.3 to 9.6 grams, depending on the brand and the labels of the priced formulas.

(3) The cost of the food consumed by the mother needed to produce the milk to feed the infant was assessed according to the actual cost of specific food items used by the United States Department of Agriculture's cost estimate of breast-feeding^{1,12}. Two spending plans were used, one moderate (M) and the other thrifty (T). The moderately priced plan consisted of 178 ml (6 oz) of orange juice, 14 g (0.5 oz) of butter, 1 L of (whole) milk, 1 egg and 2 slices of whole wheat bread¹². The thrifty plan consisted of 100 g of nonfat milk solids, 60 ml of cooking oil, 28 g (1 oz) enriched cornmeal, 150 g turnip greens (fresh), and a multivitamin and mineral supplement¹². These plans cost 53 cents and 18 cents respectively per day in 1978.

When these diet plans were analyzed using Nutritionist III software (N-Squared Computing, Silverton, Oregon, 1985), fat contributed a high proportion of total energy: About 41% and 53% respectively. Both plans were therefore modified to reduce fat, reflecting current trends in dietary recommendations. They also were modified to provide the same amount of energy, 728 kcal, and to be somewhat similar in the content of protein, calcium, and iron. To reduce fat in the M plan, butter was omitted and whole milk was changed to 2% (fluid) milk. In addition, the bread was reduced to one slice. Because fresh vegetables are costly, the fresh greens in the T plan were replaced with frozen turnip greens, the lowest-priced frozen greens in the surveyed store. Both plans (with modifications) provided 728 kcal, of which fat contributed 32% or 34% of the energy respectively (Table 1). The food items in the M plan had more cholesterol and vitamin C whereas the T plan was much higher in vitamin A (Table 1). Finally, as the nutri-

ent composition of the T plan was actually superior to the M plan for some nutrients, and the fact that multivitamin and mineral supplements are no longer routinely recommended⁹, the nonfood supplement for the T plan was omitted. Table 2 shows the actual foods and quantities for both plans.

Data collection and utilization

A Honolulu store belonging to a chain that uses the uniprice system was selected for pricing. This meant the

TABLE 1
Nutrient Composition* of Modified USDA
Food Plans for Lactation Supplement

Nutrient (weight or units)	PLAN	
	Moderate	Thrifty
Protein (g) (% energy from protein)	43.3 (24%)	40.2 (22%)
Fat (g) (% energy from fat)	26.1 (32%)	28.8 (34%)
Cholesterol (mg)	347.8	17.6
Calcium (mg)	1282.0	1359.0
Iron (mg)	2.7	3.1
Vitamin A (IU)	2455.0	9076.0
Vitamin C (mg)	82.2	23.6

*Determined with Nutritionist III software (N Squared Technology, Washington, 1985).

TABLE 2
Food Items and Cost of Modified USDA Food Plans
for 728 kcal Daily Lactation Supplement

Moderately Priced Diet Plan

Item	Portion	Cost
Orange juice, frozen, diluted	189 g	\$0.27
Milk, fluid, 2%	1 L	0.87
Egg, large, hard boiled, no shell	1	0.12
Bread, whole wheat	1 slice	0.10
TOTAL		\$1.36

Thrifty Diet Plan

Item	Portion	Cost
Milk, nonfat, instant, dried	100 g	\$0.54
Cornmeal, degermed, enriched, dry	28 L	0.06
Vegetable oil, soybean	27 g	0.07
Turnip greens, frozen, boiled	83 g	0.26
TOTAL		\$0.93

(continued on page 16)

prices for the food items were the same in 12 stores on Oahu. The store was surveyed twice, 12 months apart, for the cost of all food items. The most recent pricing was conducted in September 1990. The lowest-priced brand of each formula type (powder, concentrate, etc) was used in calculating formula costs. Two brands of formula were excluded; one was excluded because the label indicated it was for babies over 6-months of age and, therefore, was not suitable for the age group in this study. The other was omitted because it was new on the market in 1990 and had not been on the shelves in 1989.

TABLE 3

Cost of Feeding Neonate Assuming Energy Needs are the Same for Both Breast and Formula Fed Infants (108 kcal/kg)

FEEDING METHOD

Breast-fed by Mother's Diet*

Period	Formula-Fed*	Thrifty	Moderate
First 31 days	\$53.93	\$22.25	\$32.54
Second 31 days	<u>65.21</u>	<u>26.91</u>	<u>39.35</u>
Total Cost	\$119.14	\$49.16	\$71.89

*This was based on the total energy intake needed by the mother which is 21% greater than that needed by the infant. Food costs were based on the brand with the lowest per unit cost for each item. See Table 2 for a list of items.

**The cost was based on the lowest cost form and brand. Powdered formula was the lowest cost form for all brands which had more than one form. The lowest cost formula was a powdered milk-based formula. The infant needed 14,396 kcal in the first month (464 kcal/day) and 17,410 in the second month (562 kcal/day).

TABLE 4

Time Trend in Cost of Feeding a Newborn for the First 62 Days, By Food Type

ACTUAL COST*

Food Type	YEAR		Percent Increase
	1989	1990	
Formula	\$104.56	\$119.14	13.9
Breast-fed—			
Thrifty Food Plan	48.64	49.69	2.2
Breast-fed—			
Moderate Food Plan	67.67	72.42	7.0

*Cost is based on lowest cost items. The formula is a powdered milk-based infant formula.

As for the food items for breast-feeding mothers, the lowest priced brand per unit measurement was used (sale prices were excluded). In calculating the cost of breast-feeding, the actual amount of energy needed by the mother (based on the infant's energy needs plus the mother's need for an additional 21% to produce the milk) was calculated and that number was divided by the energy provided by the plan (728 kcal). This number was then multiplied by the cost of each of the 2 food plans (thrifty or moderately priced).

Results

Thirty-six proprietary milks and 29 different items for the mother's food plans were priced.

Table 3 presents the costs assuming the infant needed 108 kcal/kg, regardless of milk type. Foods for breast-feeding cost substantially less than formula, regardless of the plan (Table 2). Even the moderate plan was 39% less than the cost of the cheapest formula. The difference in cost increases substantially when the lowest-cost formula is not used. The lowest-priced concentrated formula cost \$149.86 for the 2-month period, over twice as much as the moderate food plan and 3 times the cost of the thrifty food plan. The lowest-priced ready-to-feed (RTF) formula (in 32 ounce containers) cost \$178.41, 3.6 and 2.5 times the cost of the thrifty and moderate food plans, respectively.

Table 4 shows the trend over time in feeding costs. Using the lowest-cost items, the cost increased by 13.9% in one year for formula, whereas the T and M plans only increased by 2.2 to 7.0%, respectively. Changes in costs of formula differed by formula category, however, with relatively small increases (2.5 to 2.8%) in one year for the lowest-priced concentrated and RTF formulas. Thus, while these 2 types of formula continued to cost a lot more than foods for breast-feeding, the ratio of costs did not change significantly in the 12 months of study.

Discussion

Over a decade ago, the cost of food for a newborn did not differ greatly depending on whether the infant was breast-fed or formula-fed; that is no longer the case in Hawaii today. The cost of food for the neonate in the first 62 days of life differed substantially by feeding method, the cost being much lower for the breast-fed infant. This difference exists in spite of the fact that the cost difference was probably minimized by using the lowest-priced formula and the same energy need in both breast and formula-fed infants, since there is substantial evidence that, on average, breast-fed infants need to consume less food energy as compared to formula-fed infants^{9,11}.

These relative differences in cost have significant implications for infant feeding programs that are trying to reduce cost or to minimize cost increases. In June 2, 1990, Cable News Network reporter Eugenia Halsey noted that infant formulas had nearly doubled in price since 1980. Government programs such as the United States Department of Agriculture's Supplemental Food Program for Women, Infants, and Children (WIC) have been trying to hold down costs by promoting breast-feeding, but it has been difficult to do.

Based on the cost estimates in our study, it would cost at

(continued on page 18)



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Indications: Yocon® is indicated as a sympathicolytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral alpha-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

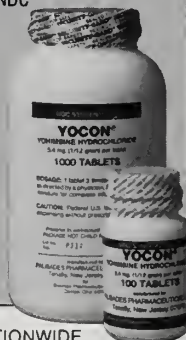
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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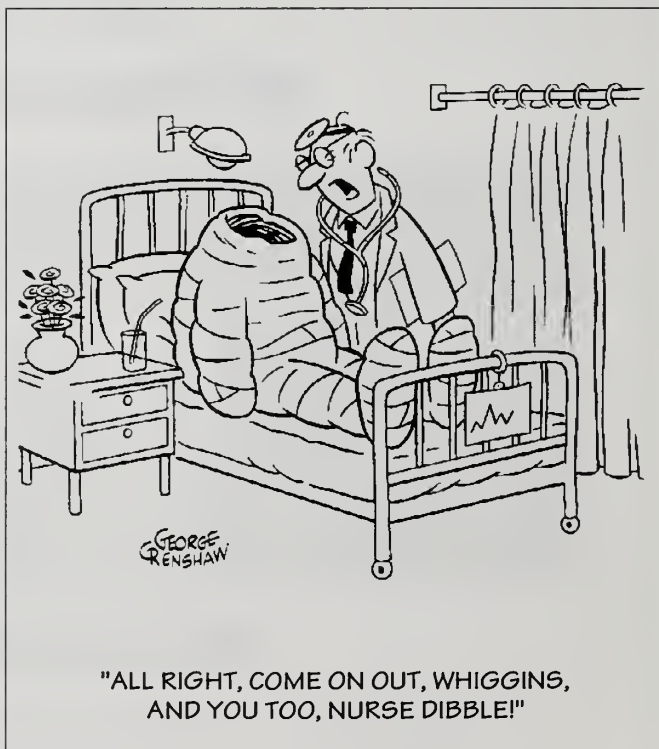
BREAST-FEEDING VERSUS FORMULA: COST COMPARISON (Continued from page 16)

least an extra \$45 to \$70 to feed a newborn formula for 62 days; put in another way, 2 newborns could be breast-fed for the cost of one newborn who is formula-fed.

Although one could argue over our assumptions, it is evident that food for the mother who breast-feeds costs considerably less than buying formula for the infant. This may be an important consideration in helping families decide what should be the first milk for the newborn baby.

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Henry N Yokoyama MD

Quotables

Straub plastic surgeon Randolph Wong introduced fellow plastic surgeon Clyde Ishii at a Straub Health Foundation-sponsored symposium on wound healing: "We make noses smaller and boobs bigger."

"Coupla cars got into a disagreement on the Pali," KUMU announcer describing the morning traffic.

Honored, Elected & Appointed

Reginald Ho, chief of Straub Oncology and Hematology, was elected 1993 American Cancer Society president. He hopes to focus on early detection of prostate cancer and pain control in cancer patients. (Reggie modestly says his main claim to fame is his son Reggie Jr who kicked 4 field goals and an extra point for a 19 to 17 Notre Dame victory over Michigan in 1988.

Ramon Sy was named the 1992 Hawaii Medical Association Physician of the Year for his 10-year work with the Aloha Medical Mission, which sends volunteer medical teams to the Philippines, China and other Pacific countries, and more recently has been treating Hawaii's own homeless. HMA President Stephen Wallach described Ramon as "a giant among his peers" and HCMS Treasurer Danelo Canete said, "Dr Sy has rekindled the good image of today's physician, tarnished by the public perception that we are pushing the limits of ethical medicine in our quest to put a Mercedes in our garage."

Pediatrician Jeanette Chang is our new HMA president. Herein are notable excerpts from her acceptance speech: "My goals for the next year are simple, but necessary for our survival...I want to make the HMA an organization to which physicians can be proud to belong—to join together in safeguarding the practice of medicine...There are many legislators and organized groups who are pushing for nationalized medicine. As you all know, any government-run system encourages mediocrity, encourages scarcity, and leads to rationing of care...Today, more than ever, physicians need an association to represent the profession and to fight for their rights...I not only want an increase in members, but I want an increase in enthusiastic members who are going to be players and not merely spectators. If I could have only one wish, I would wish for a vial of enthusiasm to inject into the veins of apathetic physicians...The practice of medicine is still the noblest of all professions, and I want to help nurture what is left of the doctor-patient relationship, instead of the provider versus consumer concept. We all have to join together because there is strength in numbers..."

The American Cancer Society Honolulu Unit named surgical oncologist Scott Hundahl president for 1992-93.

The HMA awarded Legislator of the Year awards to State Senator Andrew Levin and State Representative Duke Bainum.

Miscellany

Saddam Hussein was traveling in his limousine through a small village outside Baghdad when his chauffeur lost control and killed a donkey. Saddam ordered his chauffeur to go into the village and pay the owner of the animal. The chauffeur came back shortly loaded with gifts. "What happened?" Saddam asked. "I don't know. I went to the town square and announced that I am Saddam Hussein's driver and that I had killed the jackass."

(Submitted by Benjamin Goo and Louis Polskin)

A couple in their mid-90s were sitting in their rocking chairs and reminiscing about their life together. They had recently celebrated their 75th wedding anniversary. Wife to her husband: "You know, honey, I'm really proud of you." Husband, adjusting his hearing aid, retorted, "Yes, and I'm really tired of you, too."

As told by our humorist
Gloria Madamba

Organization of Women Leaders (OWL) gave four awards for 1992. One of the awards went to Calvin Sia for establishing the Hawaii Family Stress Center at Kapiolani Medical Center for Women and Children. The awards are given to individuals and organizations that enhanced family life in Hawaii. The other awards went to Gov John Waihee, Lt Gov Benjamin Cayetano and KHON-TV President Michael Rosenberg...

Life in These Parts

Trauma physician Peter Halford told the Hawaii Injury Prevention Conference held in October at the Hilton Hawaiian Village that the following tested positive for alcohol and drugs:



- 59% of Hawaii's traffic deaths
- 56% of persons injured in traffic accidents
- 33% of those injured in other accidents
- 53% of those injured in motorcycle accidents
- 27% of pedestrians hit by vehicles, 70% of those injured by guns, 63% injured in stab-bings and 38% injured in other mishaps
- Only 24% of motorcycle riders wearing helmets...

Professional Moves

August: Internist Malcolm Haruno (who specializes in pulmonary and critical care medicine) joined George Druger at The Queen's POB II Ste 704; Neurology Associates at 321 N Kuakini announced the retirement of Michael Okihiro and the association of David Kaku with Melvin Yee.

September: Internist David Saito relocated to Pali Momi Medical Office Bldg, Ste 350; nephrologist David Ono associated with Richard Shim and Aaron Nada at their offices at Profes-

(Continued) ➤





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sional Plaza of the Pacific, Pali Momi Medical Center and the Kailua Professional Bldg; orthoped Stephen Naruto relocated to Ste 50, Aiea Medical Bldg; Jane Service and Barbara Kitashima relocated their OB-Gyn practice to Kapiolani Medical Center, POB Ste 510.

October: Internist Timothy Ahu opened at Pali Momi Medical Office Bldg, Ste 570; Big Island psychiatrist Brooks Griffith announced his retirement and that Andrew Mebane would take over his practice at 311 Pottery Terrace, 75-5995 Kuakini Hwy, Kailua-Kona.

November: Internists Kheng See Ang and Robert Schiff relocated their independent practices to Pali Momi Medical Office Bldg, Ste 250; Lyn Lam and Barbara Warkus relocated their OB-Gyn practice to Kapiolani Medical Center, POB Ste 515; Honolulu psychiatrist Greg Yuen opened a Hilo office at 1292 Waianuenue Ave; The Physicians' Anesthesia Service Inc at Ste 306, 321 N Kuakini St (Edwin Ichiriu, Gilbert Korenaga, Neil Manago and Reid Manago) announced the addition of Michael Hee and Stanton Lum...

Miscellany II

Wake Up Call

A couple, retired for many years, always set their clock-radio for 7 am, waking to the news. One morning, their favorite romantic music from the past started playing. The husband put his arm around his wife and whispered in her ear, "Darling, if I were 40 years younger, do you know what I'd do?" "Yes," she murmured, snuggling closer, "I know what you'd do." "Tell me, sweetheart," he sighed. "What would I do?" "If you were 40 years younger," she whispered, "you'd get up and go to work!"

From *Reader's Digest* Dec '92

Sound Familiar?

After landing his first job, my oldest son wasted no time in applying for a car loan. He answered the bank officer's questions honestly and quickly, pausing only at one question: "Other source of income?"

"Mom," replied my newly independent son.

Ruth Wade (Albany, Kentucky)

From "Life In These United States"

Reader's Digest Dec '92

Silver Anniversary

The UH John A Burns School of Medicine (established in 1967) celebrated its 25th anniversary in November with an alumni open house, a symposium, a Kaiser lectureship, a Hilton Hawaiian Village banquet and an Alumni luau at the Judd House in Waikane Valley. The medical school, established as a 2-year program, expanded to a 4-year school in 1973 and graduated its first 4-year class in 1975. At present, only 56 students are admitted annually from an applicant pool of 1,420. The alumni total 1,216 with 1,085 graduating from the 4-year program. Slightly less than 50% of the graduates practice in Hawaii. It became the first U.S. medical school to convert to problem-based learning in 1989. Each year is divided into 5 units of 12 to 16 weeks each. With problem-based learning, 5 to 6 students meet in tutorial groups with a faculty member. Educators, realizing the huge volume of information, have been discussing new approaches and problem-based learning is one approach. The students become independent learners; they no longer just memorize, but learn where to go for information.

More Miscellany

A priest and a rabbi were good friends and would discuss the many problems of the universe and especially of heaven and hell...They pledged to each other that whoever got to heaven first would return and report...The priest died first...Several months later, the rabbi saw an apparition... "Hello! Hello! Is that you, Marsh?" "Yes, it is I." "Quick, tell me how things are..." "Well, I sleep late...Grab a leisurely breakfast and then make love...I nap till noon...After lunch I make more love...I nap again till dinner time...After dinner, I make love again till bedtime." The rabbi was getting quite excited. "Marsh, that doesn't sound like heaven...Just where are you?" "No, it's not heaven, but I sure am in paradise...I'm a buffalo bull in Utah."

(As told by George Sacks, VP from UCLA, who lectured on Acid Pump Inhibitors at a UH Merck-sponsored GI Symposium on Nov 13)

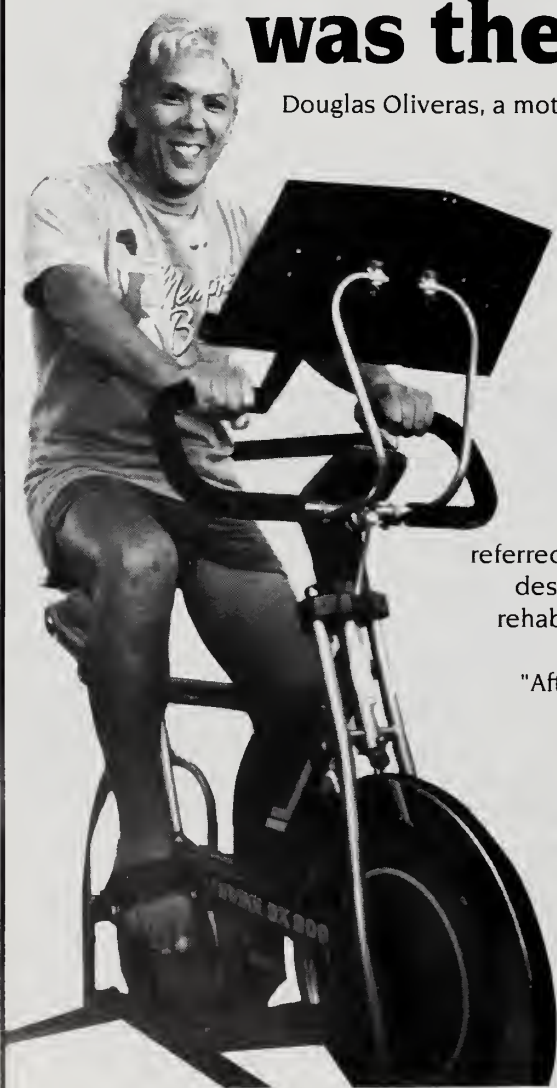
"CHART's program was the best!"

Douglas Oliveras, a motion picture cameraman, was moving some heavy camera cases when he badly twisted his knee.

"My knee was really swollen, and I couldn't walk or even bend my knee," Douglas recalls. "I had shots to kill the pain and I took anti-inflammatory pills."

Three weeks after his accident, Douglas was referred to CHART for a custom designed program of active rehabilitation and total body reconditioning.

"After about seven to eight weeks of CHART's treatment, I went right back to work," Douglas says. "I've had physical therapy before for my back and legs, but CHART's program was the best I've ever seen!"



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Hors de Combat

Attorney General Warren Price estimates that 5% to 10% of the state Medicaid's \$340-million expenditure is wasted or lost to fraud annually...He reported that the Pay 'n Save drugstores avoided state criminal sanction by paying a \$1-million fine (for bilking the Medicaid program between 1987 and 1991) but may still face federal prosecution. The AG applauded the work by his 16-member Medicaid Investigations Division, which studied reams of computer printouts seized from Pay 'n

Save. Deputy AG Dewey Kim Jr says the investigation covered 15 island stores which defrauded Medicaid by incorrect billing, such as charging regular rather than bulk-purchase prices, and double charges, such as filing claims for refills when patients did not request refills.

Benjamin Spock, 89, spoke in Boston (with representatives of the Physicians Committee for Responsible Medicine): "Children should be breast-fed if possible to age 2. After 2, forget milk of any kind altogether." The group warns against feeding

milk to children because of low iron, high fat and possible contamination with antibiotics or Vit D. Both dairy farmers and the AMA contend he is wrong about milk.

Mission Accomplished

The 10th Aloha Medical Mission (90 volunteers with 60 from Hawaii) returned after treating 10,000 people in Baguio, Iloilo and Zambales on Luzon, according to Ramon Sy, mission organizer and president. All volunteers paid their own way and their services were given free of charge. Ophthalmologist Jorge Camara (on his 5th mission) reported that the mission performed over 90 eye operations. In Hawaii, the Aloha Medical Mission provides free medical care to the homeless. The Mission is currently planning missions to Viet Nam, China and areas in the South Pacific and Micronesia.

Sexism in Medical Care?

The RAND Corporation examined data on 11,242 elderly treated for congestive heart failure, heart attacks, pneumonia and strokes at 297 hospitals during the periods, 1981 to 1982 and 1985 to 1986. The Corp reported that in general elderly men and women received roughly equal treatment. There was a slight bias against women: Women failed to get needed diagnostic tests slightly more often than men; men received more care than women; and men were favored in the use of expensive, high-tech services.

NINTENDO

Hygienic warfare, come of age
Resembling games on a playroom stage.
Targets drawn on video screen
Where human flesh is never seen.

The vehicles involved have target scopes,
And moving weapons, the player hopes,
Will destroy the "alien's" wicked force
With shrieks of joy and no remorse—

Amassing hits and tallying score
And when it's over we want for more.
Sounds of weapons with rapid fire
Add to the thrill of "guns for hire."

For only a quarter slid in a slot
You purchase a war where no bodies rot.
Five minutes of fun, of eye to hand skills,
Then read in bright lights your number of kills.

Another option today exists
To fighting battles with bullets and fists
Besides two bits for a video game
You can play it removed as you test
out your aim!

It's much the same as video
If you like to play it just join up and go!
The taxes collected the last decade
Built a world of Nintendo and the fare is paid.

Laser marked targets from land or air
Guide "home" the missiles that you
launch from a chair.
"Hell fires" and "Spritzers" to name just two
And it's awfully exciting to watch what they do!

They go through vents, through shafts
and doors
To blow up their scuds and blast ammo stores
Night scopes fixed on tanks and apaches
Sleuth out "rats" the "cat" then catches—

Scopes with videos and long distance beams
Remove us from targets and therefore it seems
Abstract and lifeless like figures in a creche,
And so far away that you don't smell
burned flesh.

The enemy helps by removing from sight
Their dead and dismembered: They're buried
at night

To hide from their own the death that
we've wrought
With new space age weapons our taxes
have bought!

But pause valiant soldiers of Nintendo art
And know those are humans we're
blowing apart
Fathers and husbands, lovers, and sons—
Each precious to God...and to some
other ones.

Pause valiant pilots to reflect on the kill.
Picture the blood each missile will spill.
Pause, tank commander, look close and learn
How awful it feels to have your flesh burn.

Pause at your cannons for vet'rans
remembered,
And think on the plight of those
who've dismembered.—
On beautiful life when it's snuffed out
in youth...
On love and compassion as ultimate truth.

I suppose there are wars that have
to be fought,
And perhaps there are weapons it's good
that we bought,
And maybe in battles some lives must be lost
But, God, in your mercy, how awful that cost!

Hygienic and tidy? It seems so unreal;
Removed from the victims you don't have
to feel!
Pain or remorse at lost life and grief?
It hardly seems more than when trees shed
a leaf.

But know them as humans who love and
who hurt,
And think on their spouses as they're laid
down in dirt—
Perceive them as parents, and not through
a scope...
And you'll pray hard for peace...and never
lose hope!

Robert S Flowers
February-March, 1991

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EMPLOYMENT OPPORTUNITY

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PRACTICE FOR SALE — General Internist retiring in March 1993 after 34 years of active practice. South King Street near NBC Concert Hall. Good patients and reasonable terms. Call 538-7886.

A REAL BARGAIN — Closing branch office in Waipahu; willing to leave office improvements and furniture (chairs, exam. table, typewriter, refrig., copier, cabinets, phone, etc) for \$3000 or best offer. Call 523-9677, 521-8288 or 523-7955.

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CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in ALT and AST equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Alcohol should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids (1 hour prior to PRAVACHOL), cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs: During clinical trials, no noticeable drug-drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a \geq 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spiroglactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinoganglionate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulo-ocular Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/– mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: **Pregnancy Category X:** See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (fetus) or 240x (rat) the human exposure based on surface area (mg/m²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthena, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

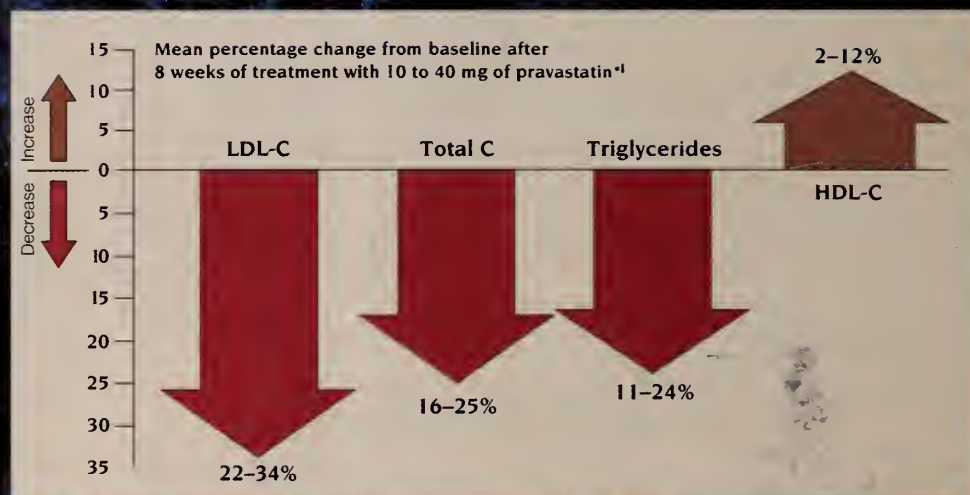
Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. (J4-422A)





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¹Each arrow represents a range of means derived from a single placebo-controlled study that included 55 patients treated with pravastatin.

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.


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Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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Highlights of the HMA Council Meeting of January 8, 1993

The HMA Council met on 8 January 1993. The highlights of its action follow. Members present were: J Chang, A Don, J Spangler, S Wallach, C Kam, R Stodd, P Blanchette, C Lehman, B Shitamoto, R Lee-Ching, M Chen, R Goodale, HKW Chin, P Chinn, HH Chun, W Dang, Jr, P Hellreich, S Hundahl, R Kimura, A Kunimoto, M Shirasu, K Thorburn, C Kadooka, J Betwee, H Percy, T Smith, G Goto, J Lumeng, W Chang, N Winn, W Dang, J McDonnell; F Reppun, Editor, *HMJ*; Legal Counsel Vernon Woo; Auxiliary representative, Susan Spangler; HMA Staff: J Won, L Tong, J Asato, J Estioko and A Rogness (recording secretary).

President Chang announced that the tremendous holiday gathering on Kauai, hosted by the HMA for the Kauai physicians to honor their steadfast duty during Hurricane Iniki, was a success.

The HMA position statement on Availability of Care adopted at the previous meeting of Council was rescinded in favor of an existing policy statement of the AMA, Section 130.970(1) of the Policy Compendium, 1992, as follows:

"All physicians and health care facilities have an ethical obligation and moral responsibility to provide needed medical attention to all emergency patients presenting at the emergency department, regardless of their ability to pay."

Council members voted to endorse their HMA colleague, Jack Lewin, for the position of Assistant Secretary of the U.S. Department of Health and Human Services, or any other position within the federal government should he be offered such a position.

The Ad hoc committee recommendation on HMA's position on prescriptive authority for advanced registered nurse practitioners was discussed fully. Ensuing substitute and alternative motions were offered and the final statement was adopted to read as follows:

"The HMA opposes any nurse prescriptive authority legislation that compromises the public's safety and its quality of medical care, which is what has been presented thus far. The HMA has always been open to, and continues to be open to, negotiations for proper and appropriate legislation in this area as we have demonstrated in our meetings with the Hawaii Nurses Association but have been turned down by the HNA."

Two seminars were announced—one by Ms. Rhoda Weiss, practice management consultant, on tips for running a better office; another via member benefit company First Hawaiian Bank on "Collections at Point of Service."

A reception for legislators hosted by the HMA is scheduled for February 1, 1993.

Fred Holschuh
Secretary



I enjoyed the article concerning prenatal care of the gestational diabetic patient at the Waianae Coast Comprehensive Health Center (WCCHC) in the November *Hawaii Medical Journal*. Your editorial review of the article was refreshing and helps to reinforce the credibility of those of us who practice medicine in "rural Oahu".

Gestational diabetes is one of many diseases requiring close physician/patient coordination and communication. This will always be much more successfully accomplished in the patients' living area. The WCCHC is an excellent role model for preventive and outreach programs.

However, I would like to correct a significant inaccuracy in your editorial. St. Francis Medical Center-West commenced inpatient obstetric care in April 1991, and the growth has been consistent. There were 75 deliveries at St. Francis Medical Center-West in 1991, and 263 in 1992 performed by our staff of nine obstetricians. As predicted by the St. Francis Medical Center-West

Administration, many WCCHC, Ewa plain and Makakilo patients prefer locally available obstetric care and delivery. Prenatal care compliance will always be improved with obstetric care available at the local level.

James F Lyons MD
Chair, Department of Ob-Gyn
St. Francis Medical Center-West

The editor replies:

Our apologies to St. Francis Medical Center-West for stating in our editorial in the November 1992 issue of the *Journal* on page 296, that "there are no facilities in the Waianae region, or anywhere closer than KMCWC..." Dr. Humphrey's article on gestational diabetes described a particular relationship between the WCCHC and KMCWC, a tertiary facility.

J I Frederick Reppun
Editor



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a limb.

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Pulmonary Balloon Dilation for Valvular and Arterial Stenosis

Edgar C K Ho MD*

The use of balloon catheters to dilate obstructed vascular lesions represents one of the major advances in cardiology and dates back to 1964 when Dotter and Judkins³ reported their experience in dilating arteriosclerotic obstructive lesions. Since that time, the technique of balloon dilation has been used extensively for coronary and peripheral vascular lesions but also has been applied to such diverse cardiac lesions as pulmonic stenosis, mitral stenosis, aortic stenosis, aortic coarctation, superior vena caval and pulmonary venous obstructions.

Balloon dilation has been used for both valvular and arterial pulmonary stenosis¹⁰. The purpose of this study is to report on our initial experience in Hawaii with balloon dilation of valvular pulmonic stenosis and also with dilation of peripheral pulmonary artery stenosis due to congenital causes and as a residual postoperative lesion.

Introduction

In the field of pediatric cardiology, the first use of a balloon dilation catheter was for valvular pulmonic stenosis⁴. In 1982, Dr. Jean Kan at the Johns Hopkins University School of Medicine used a balloon catheter to successfully dilate the pulmonic valve in an 8-year-old patient. Since that time, there have been other cases reported in the world literature^{2,5,6,9,14,15,18,19,21}. As experience accumulated, it became evident that this technique was effective, safe, and had many advantages over surgical valvotomy. Today, balloon valvuloplasty is considered to be the treatment of choice for valvular pulmonic stenosis⁸.

Pulmonic stenosis can be divided into valvular, subvalvular and supravulvar stenosis. Supravulvar pulmonic stenosis can be divided into those lesions involving the main pulmonary artery, or either of the main branches or smaller peripheral pulmonary artery branches.

Valvular pulmonic stenosis is one of the more common congenital heart anomalies, occurring in 8% to 10% of patients with congenital heart disease¹. Supravulvar pulmonary artery stenosis is less common than valvular stenosis and occurs in only 2% to 3% of all patients with congenital heart disease¹¹.

Methods

A standard cardiac catheterization and cineangiocardiology is performed to measure the valvular pressure gradient and the diameter of the valve annulus. After heparinization, a balloon catheter is introduced over a guide wire and the center of the balloon is positioned over the valve. The balloon size selected is 20% to 40% larger than the diameter of the valve annulus. The balloon is inflated with dilute contrast material with up to 5

atmospheres of pressure for a duration of up to 15 seconds to achieve the elimination of the "waist" in the balloon which represents the constriction of the balloon by the stenotic valve. During inflation, the arterial blood pressure and electrocardiogram are monitored. After valvuloplasty, the pressure gradient and cineangiocardiology are repeated.

The same technique is used for peripheral pulmonary artery stenosis except that the balloon sizes are up to 4 times the diameter of the obstructed artery segment and inflation pressures are higher.

Results

The first case was a 5-year-old girl who was born with Tetralogy of Fallot. She had a large ventricular septal defect and severe valvular pulmonic stenosis requiring a Blalock-Taussig shunt in early infancy to provide adequate pulmonary blood flow. At age 3 years, she underwent total correction of her Tetralogy of Fallot. The pulmonary valve annulus was very constricting and a transannular patch had to be used to enlarge the pulmonary artery.

Several years after her surgery, she developed a significant residual pulmonary obstruction at the site of the transannular patch. At cardiac catheterization, the right ventricular pressure was 139 mm Hg and the gradient across the obstruction was 110 mm Hg.

A 12 mm balloon was selected for the dilation after which the right ventricular pressure was reduced to 86 mm Hg and the gradient was reduced to 58 mm Hg. Followup Doppler echocardiography revealed a persistent 54 mm Hg systolic gradient.

A repeat angioplasty 9 months later using a larger 20 mm balloon failed to reduce the gradient further, and she was referred for surgery. At surgery, the patch was extended to the bifurcation of the branch pulmonary arteries. Postoperative Doppler examination revealed a reduction of the gradient to 36 mm Hg.

The second case was a 16-year-old girl who was born in the Philippines with a large atrial septal defect and severe valvular pulmonic stenosis. After immigrating to Hawaii at age 12 years, she was found to be severely symptomatic.

The atrial septal defect was closed at 13 years of age, and at the same time, a valvotomy was performed.

She was reevaluated by Doppler echocardiography 2 years after surgery and was found to have a significant residual pulmonic gradient. At cardiac catheterization, the right ventricular pressure was 110 mm Hg and the valve gradient was 96 mm Hg. The subvalvular infundibular area was also hypertrophied. An 18 mm balloon was used for the dilation after which the right ventricular pressure decreased to 50 mm Hg and the gradient to 38 mm Hg.

One year later, Doppler echocardiography demonstrated an increase of the gradient to 60 mm Hg. A repeat cardiac

* Pediatric Cardiology
Straub Clinic & Hospital, Inc.
Submitted for publication November 1991.

(Continued on page 32) ►



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catheterization confirmed a gradient of 58 mm Hg. Dilation was performed with a 23 mm balloon, reducing the gradient Hg. Three months later, the gradient by Doppler echocardiography remained at 14 mm Hg.

The third case was a 9-year-old boy also born with Tetralogy of Fallot with an absent pulmonary valve and hypoplasia of the pulmonic annulus. At 3 years of age, he had a total correction and a transannular patch was used to relieve the pulmonic stenosis.

Three years after surgery, cardiac catheterization revealed severe residual pulmonic stenosis, and he then had an aortic homograft inserted into the right ventricle with the distal end connected to the main pulmonary artery, bypassing the obstructed annulus.

At 9 years of age, cardiac catheterization identified an obstruction at the junction of the homograft with the main pulmonary artery. The right ventricular pressure was 89 mm Hg and the gradient across the stenosis was 47 mm Hg. After dilation with a 20 mm balloon, the right ventricular pressure decreased to 42 mm Hg and the gradient was reduced to 4 mm Hg.

One year later the right ventricular pressure had again increased to 82 mm Hg and the gradient to 56 mm Hg by catheterization. The patient is awaiting surgical angioplasty; it appears the stenosis was relieved only temporarily by the dilation.

The fourth case was a 14-month-old boy with a combined valvular and supra-valvular stenosis. At cardiac catheterization, the right ventricular pressure was 72 mm Hg, the supra-valvular gradient was 29 mm Hg and the valvular gradient was 36 mm Hg. Balloon dilation eliminated the valvular gradient and reduced the supra-valvular stenosis to 22 mm Hg. It is hoped the small, residual supra-valvular gradient will remain so as he grows.

The fifth case was a 7-year-old boy who had his Tetralogy of Fallot repaired at 2 years of age, requiring a transannular patch for a hypoplastic pulmonary annulus. Postoperative Doppler echocardiograms demonstrated a progressive increase in the systolic gradient across the pulmonary outflow tract. At cardiac catheterization, the gradient measured 36 mm Hg. Because of the large diameter of the pulmonary annulus, balloon angioplasty was performed using the double-balloon technique²¹. The 2 balloons were inflated simultaneously and produced a total balloon diameter of 30 mm; the post-dilation gradient was 26 mm Hg.

Discussion

Several years after the first report by Kan, it became obvious based on the numerous reports from large medical centers throughout the world that pulmonary balloon valvuloplasty was effective in relieving valvular stenosis and is the procedure of choice over surgical valvotomy; it can be carried out safely in regional hospitals. Although not as successful, dilation of peripheral pulmonary artery obstructions also have been accomplished. Recently 5 cases were treated at Straub Clinic & Hospital, the first cases of balloon pulmonary valvulo/angioplasty performed in Hawaii. These cases also demonstrate the different clinical situations in which this technique is applicable; that is, valvular stenosis, congenital pulmonary artery stenosis, and postoperative pulmonary artery stenosis.

The indication for balloon valvuloplasty is the same as for surgical valvotomy; that is, a systolic gradient in excess of 50 mm Hg. There have been recent recommendations to lower this

criterion to 35 mm Hg¹⁶, primarily because the procedure is relatively noninvasive as compared to surgery, and because an obstruction severe enough to result in a 35 mm Hg gradient might eventually result in irreversible right-ventricular cardiomyopathy.

Complications have been few and are listed in Table 1. Selecting the proper catheter size helps to avoid injury to the vessel wall. Arrhythmias and transient hypotension do occur and are associated with the balloon inflation, but resolve rapidly afterward. Unless there is a significant injury inadvertent to the myocardium, there usually are no other significant arrhythmias.

Cumulative results from some of the larger series reported elsewhere^{5,9,15,16,17,18} and comparison with results of surgical valvulotomy¹³ are shown in Table 2. The operative mortality is comparable, with valvuloplasty appearing to have the edge over surgical valvotomy when all ages are considered.

Initially when the size of the balloons used was limited to the diameter of the valve annulus, 60% to 70% of patients had significant residual gradients greater than 25 mm Hg^{6,20}. It then was demonstrated that balloon sizes up to 40% larger than the valve annulus diameter could be used safely and results improved with only 7% to 11% of patients having significant residual gradients. The pulmonic regurgitation resulting after either surgical valvotomy or balloon valvuloplasty is usually mild and clinically not significant.

In patients with peripheral pulmonary artery stenosis, approximately 55% of the vessels are successfully dilated with an increase in angiographic diameter by over 50%⁸.

Table 3 summarizes the results of Straub's 5 cases.

Valvular stenosis is relieved by the balloon tearing tissue along the path of least resistance by splitting the fused commissures or by tearing through the cusp itself, and sometimes by avulsion of the cusp from the annulus²⁰. In our 2 cases with valvular stenosis, the gradients across the valve were significantly reduced and postvalvuloplasty cineangiograms demonstrated increased systolic valve opening.

Dilation of congenital peripheral pulmonary artery stenosis is probably accomplished in much the same manner as dilation of coarctation of the aorta; that is, by tearing of the intima⁷. However restenosis can occur with accumulation of fibrous tissue in the healing process. In our patient with a combination of valvular and supra-valvular stenosis, the latter obstruction was partially relieved by dilation.

There are few reports of results following dilation of postoperative residual pulmonary artery stenosis. In our first patient, who had repair of a Tetralogy of Fallot and who developed a residual stenosis at the area of the transannular patch, tearing fibrous tissue within the patch may have been the mechanism responsible for the partial reduction of the obstruction. However, the discrepancy in size between the dilated proximal and narrow distal main pulmonary artery was not remediable to further balloon dilation and the patient required further surgery.

The patient with the aortic homograft obstruction appears to have had only a temporary successful result. In his situation, the stenotic area may have been stretched but gradually recoiled to its previous state.

Repeat catheterization of some of these patients in the future will enable us to evaluate the long-term results of balloon dilation and the ability of this technique to permanently relieve obstruction of pulmonary valves and arteries.

Summary

Five patients with a combined experience of pulmonary valvular stenosis (2 cases), congenital supravalvular stenosis (1 case), and postoperative residual pulmonary artery stenosis (3 cases) are presented along with the results of balloon dilation of these lesions. Balloon dilation was successful in the 2 valvular lesions, partially successful in 1 patient with supravalvular stenosis, and helpful in 1 out of 3 patients with postoperative pulmonary artery stenosis. Balloon dilation is the treatment of choice in valvular pulmonic stenosis and may be helpful in congenital and acquired pulmonary artery obstructions.

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TABLE 1. Potential complications of balloon dilation

- Rupture of the pulmonary artery.
- Contusion to the right ventricular outflow tract.
- Transient hypotension.
- Ventricular ectopic beats during balloon inflation.

TABLE 2. Comparative results of surgical valvotomy and balloon valvuloplasty for valvular pulmonic stenosis

	Surgery		Valvuloplasty
Mortality	< 10% < 2 yrs < 0.5% > 2 yrs		< 0.5% all ages
Residual gradient < 25 mm Hg.	81%		89 - 93%
Residual pulmonic regurgitation	50%		20%

TABLE 3. Results of balloon dilation

	Before		After		RV Press Reduction %	PA Grad Reduction %
	RV Press MM HG	PA GRAD MM HG	RV Press MM HG	PA Grad MM HG		
Case #1 (A)	139	110	86	58	38	47
Case #2 (V)	105	58	94	54	10	7
	71	58	32	14	55	60
Case #3 (H)	89	47	42	24	53	49
	82	56				
Case #4 (V,S)	72	36 v	46	0 v	36	100 v
		29 s		22 s		24 s
Case #5 (A)	58	36	46	26	21	28
A= artery V= valve H= homograft S= supravalvular						

Quality improvement: How does it differ from quality assurance?

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Quality improvement? How does it differ from Quality assurance? The "Total Quality Management" movement which has been so successful in improving the quality of manufactured products in Japan and more recently in the United States has arrived in American service industries, including health care. Although a minority of health care institutions has adopted the Continuous Quality Improvement (CQI) or Total Quality Management (TQM) philosophy and techniques on their own, the new Joint Commission on Accreditation of Health Care Organizations (JCAHO) standards to be phased in over the next 3 years require all accredited hospitals to "adopt the new philosophy"¹.

Introduction

This article is intended to familiarize physicians with the philosophy of CQI/TQM as it contrasts with and relates to the approach called Quality Assurance (QA) with which we have become familiar in various phases of its evolution over the past 15 years².

In CQI/TQM there is a broader scope than the purely clinical scope of QA; however, this will not be addressed here. For those who are interested in the broader scope of CQI/TQM in administrative processes, planning and organizational integration, the reader is referred to Mizuno³ and King⁴.

Another caveat about the focus of this paper is the use of the heuristic device of contrasting QA and CQI somewhat to the disadvantage of QA. The authors would like to apologize in advance for any slight or offense this may cause to QA advocates. The inspection model of quality control (which is called QA in health care) provides an excellent basis for understanding CQI.

Discussion

The summary of 9 differences between QA (the old way) and CQI (the new way) represented in Table 1 forms the core for the structure of this paper. Each of the 9 differences is stated below as an action to be taken by everyone in the organization.

1. Focus on all processes, not just clinical processes.

In the past, the focus of QA has been clinical care. In an industry that is as interdisciplinary as health care, the focus must

be on all types of care and service, not just clinical care. This more comprehensive concept of quality will require "cultivation" by senior leadership, since it requires that improvement be the responsibility of all personnel, not just those designated as "QA personnel" and not just those rendering clinical care to the patient.

For this change in focus to occur, a culture of CQI needs to be cultivated in the entire work environment by the direct advocacy and participation of top leaders in the organization.

2. Eliminate dichotomous standards (met/not met) and continuously improve beyond present performance.

In the past, we have accepted that there is an objective goal (a threshold for a minimum or a "gold standard" as a maximum so to speak) for every process of care. In clinical processes of care, peer reviewers have been asked to evaluate whether or not the "standard" was met. If the standard was met, change did not need to occur.

This is not the case with CQI, where continuous improvement above and beyond any current performance is the goal. The implementation of CQI requires that leadership initiate actions that will allow all personnel to adopt the new way of thinking. These actions include allocating a training and education budget to provide the workforce with a new set of skills (for example, group process and statistical thinking skills) required by CQI.

In addition, top management needs to identify actual best performance (called benchmarking) of competitive organizations and compare internal operations with these high-performance organizations.

3. Cease attributing performance to individuals and look at the overall performance of processes and systems.

Individuals are responsible for only 15% of the variation in processes and outcomes. The system worked in is responsible for the other 85% of variation⁵. Therefore, health care organizations can improve patient care quality—ie, increase the probability of desired outcomes of the care of the patients—by assessing and improving the operational work processes (managerial, clinical, and support processes) that most affect outcomes. This defocusing of individual performance may come as a disappointment (or a relief!) to physicians who believe they are the major determinant of quality in patient care.

Quality Assurance has focused almost exclusively on the performance of individuals rather than on how well the processes in which the individuals participate are guiding them.

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4. Strive to improve the average rather than to eliminate "bad apples"⁶.

In order to "improve the average" the focus cannot be exclusively on deviant individuals. For example, when opportunities for improvement have been identified by Quality Assurance, practitioners and departments routinely spotlight the individual closest to the process, and the individual is counseled or "educated." This is not the way to go. Recognizing that 85% of variation is due to "the system", our focus instead must be on improving the process. Unfortunately, improving the process is often more difficult than "educating" the individual. Fortunately, well-established tools are available to assist in the improvement of this process⁷.

5. Cease focusing on problems and take advantage of opportunities everywhere for incremental improvement.

Quality Assurance has been the responsibility of Quality Assurance Programs and a small staff of workers. Using established review criteria these workers identify problems requiring peer review or committee review. If problems are not identified using quality review criteria, it is assumed that good quality care is provided and there is no need to change what we do or how we do it. Simply put, "If it ain't broke, don't fix it" has been our approach.

There are many limitations to this approach. First, only a few workers are monitoring the efforts of many. Second, the workers closest to the delivery of care are not in a position to identify areas for improvement or to improve processes they know do not work well. Opportunities are everywhere for incremental change, and every worker must be empowered to participate in the quality improvement effort.

6. Everyone and every process can improve; quality is everyone's responsibility.

The concept of Kaizen⁸, or "continuous incremental improvement," is how CQI achieves organization-wide improvement over time. No matter how well a person does, he or she should be preparing and attempting to do better. Maintaining quality no longer should mean "searching for bad apples"; but rather, to teach and lead employees to monitor their own performance and take action to improve everywhere.

In making the transition from QA to CQI, depending on the Quality Assurance Program to improve quality must cease. Every employee should be encouraged to take action to improve the quality of care/service. This will require each of us to evaluate our own process and outcome variables rather than relying on QA "inspectors" to measure our processes and outcomes for us. Again, opportunities are everywhere for incremental change, but every worker must be empowered to participate in the quality improvement effort.

7. "Design in" improvements to prevent errors rather than depend on inspection to detect errors.

Quality assurance activities focus on the detection of errors by inspection using pre-established criteria. Review criteria are generic, insensitive, and frequently are applied to all hospital patients. It should not be surprising that "problems" identified by using these generic screening criteria have resulted in time-consuming and costly efforts to determine what is causing the

TABLE 1. Comparison of Traditional QA ("The Old Way") to CQI ("The New Way").

"The Old Way"

- Focus is on clinical structures, process and outcomes.
- Dichotomous standards and norms (quality or nonquality, does or doesn't meet standard, guilty or not guilty).
- Individual or departmental performance.
- Statistical outliers ("Bad apples").
- Problems. ("If it ain't broke, don't fix it".)
- Done by QA staff, physician advisors, peer review meetings, and quality assurance committees.
- Detection of errors by inspection and sampling (reactive).
- Solutions generated by providers and managers (usually in a committee meeting).
- Motivated by regulatory compliance (JCAHO) and risk management.

The New Way

- Focus on all processes, not just clinical processes.
- A continuous gradation of performance from present achievement to meeting world-class benchmarks.
- Performance of processes and systems.
- Improving the average.
- Opportunities everywhere for incremental change (Kaizen).
- Done by everyone in the organization.
- Designing-in improvements to prevent errors (proactive).
- Customers (internal and external) involved in design and evaluation of solutions.
- Motivated by the need to succeed (rather than just survive) in an increasingly competitive and hostile environment.

problem. Sometimes the cause of "the problem" is never determined or "the problem" is not considered to be a "problem"; instead, the criteria are criticized, not taking into account the severity of the patient's illness or the characteristics of the particular patient.

If we continue to depend on inspection only, our efforts at improving quality will be ineffective. We need to build quality "in" not inspect bad quality "out".

8. Involve patients, staff, others, in the design and evaluation of solutions.

In the current framework of QA, patient feedback is not systematically collected and thus the patient population factor is not in the equation. When it is, the sample size and/or return rate is often so small that the results are again not representative and as a consequence are frequently discounted (especially if negative).

Patient feedback needs to be encouraged. Standardized survey tools (which are reliable and valid) and techniques must be used to measure both patient satisfaction and patient outcome health status. More informal methods can be used to obtain internal patient input on specific processes being studied for improvement.

9. An orientation toward success, rather than compliance with regulations will motivate us.

Quality Assurance was too often externally driven (by the JCAHO among others) in order to meet outside requirements. If quality is driven only by coercive outside forces, our focus will be to meet the requirements of such agencies. The culture of continuous quality improvement must be fostered in our work environment since our obligation to our patients never ceases.

Conclusion

As our understanding of how to improve the quality of our services to patients and thereby improve their health status continues to evolve, there undoubtedly will be a time in the future when QI is viewed as "the old way" and another "new way" will have been born. There are already some indicators on the horizon that suggest "systems thinking" can supplement and complement total quality management. In health care this could lead to our looking beyond the acute care process and linking health care organizations with our communities through education for health (at all ages), designing processes that prevent environmental degradation, and fostering social and family relationships that can help prevent the many causes of maladaptation and psychosocial distress that are so prominent as causes of illness today.

Although self-referential statements are often frowned upon, continuous improvement of continuous quality improvement doesn't seem like such an unlikely occurrence.

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Vaginal Birth After Cesarean Section in Hawaii Experience at Kapiolani Medical Center for Women and Children

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Medical records at Kapiolani Medical Center for Women and Children were reviewed for cases that had a trial of labor subsequent to prior cesarean section during the period January 1990 to July 1991. All cases were \geq delivered 36 weeks' gestation. During the 19-month period, 356/483 or 73.5% cases with a trial of labor had successful vaginal births after previous cesarean sections (VBAC). The majority of the others that did not were due to failure of progression in labor. The incidence of scar separation was 5/483 (1.04%). There were 5/483 neonates with Apgar scores of ≤ 6 at 5 minutes, giving a perinatal morbidity rate of 1.04%. There were no maternal deaths. Oxytocin induction resulted in successful VBAC in 30/47 (63.8%) cases. This study concludes that a trial of labor for vaginal birth after cesarean section is well established at our institution. In addition, the rates of successful VBAC, its complications and outcomes, are comparable to national averages.

Introduction

The dictum "once a cesarean, always a cesarean" was stated by Dr. Edwin Craig in 1916¹. This was applied in an attempt to avert catastrophic maternal and fetal loss associated with uterine rupture during labor². In the United States, no maternal death from a ruptured lower-segment cesarean scar has been reported for more than 20 years³⁻¹. Almost 1-million cesarean sections (C-sections) are performed in the United States annually and the single most-common indication for major surgery has been elective, repeat, cesarean sections⁴. In terms of the ever-rising cost of medicine, it is estimated that a 1% reduction in the C-section rate would save nearly \$27 million a year⁵. In 1982, the American College of Obstetricians and Gynecologists (ACOG) published its first guidelines for vaginal birth after C-section (VBAC)⁷. The ACOG paper summarizes the data of VBAC statistics using ACOG guidelines at Kapiolani Medical Center for Women and Children (KMCWC) from January 1990 to July 1991.

Patients and methods

Data on labor, delivery and maternal and neonatal outcomes were obtained from the "final diagnosis" records of women ≥ 36 weeks' gestation with a history of previous C-section who were delivered vaginally in January 1990 to July 1991. Thirty-six weeks' gestation was chosen as the cut-off to eliminate prematurity as a complicating factor. Data recorded included: Success or failure of the VBAC attempt, indication for repeat cesarean, method of vaginal delivery (spontaneous or operative), incidence of perineal lacerations, incidence of uterine scar separation, Apgar scores, twin deliveries, breech deliveries, shoulder dystocias, and the use of Oxytocin for induction of labor. Deliveries were performed by attending physicians or by supervised residents of all levels.

During the period January 1990 to July 1991, there were 748 patients with a history of previous C-section (Table 1). Of the patients who underwent a trial of labor, 346/483 were delivered vaginally, giving a successful VBAC rate of 73.7%; the other 127/483 (26.3%) patients required a repeat C-section. Indications for repeat cesarean in the failed trial-of-labor group included: Failure to progress, fetal distress, cord prolapse and preeclampsia (Table 2).

Of the 356 successful VBAC patients, 274 (77%) gave birth spontaneously; 82 (23%) required an operative delivery *per vaginam* with vacuum or forceps. All patients who developed a third or fourth degree laceration, vaginal vault laceration, or cervical laceration which required repair were included in this study. The incidence of perineal laceration in the women delivering spontaneously was 17/274 (6.2%), and in the case of operative deliveries was 12/82 (14.6%). The overall incidence of significant perineal lacerations in the VBAC patients was 29/356 (8.1%).

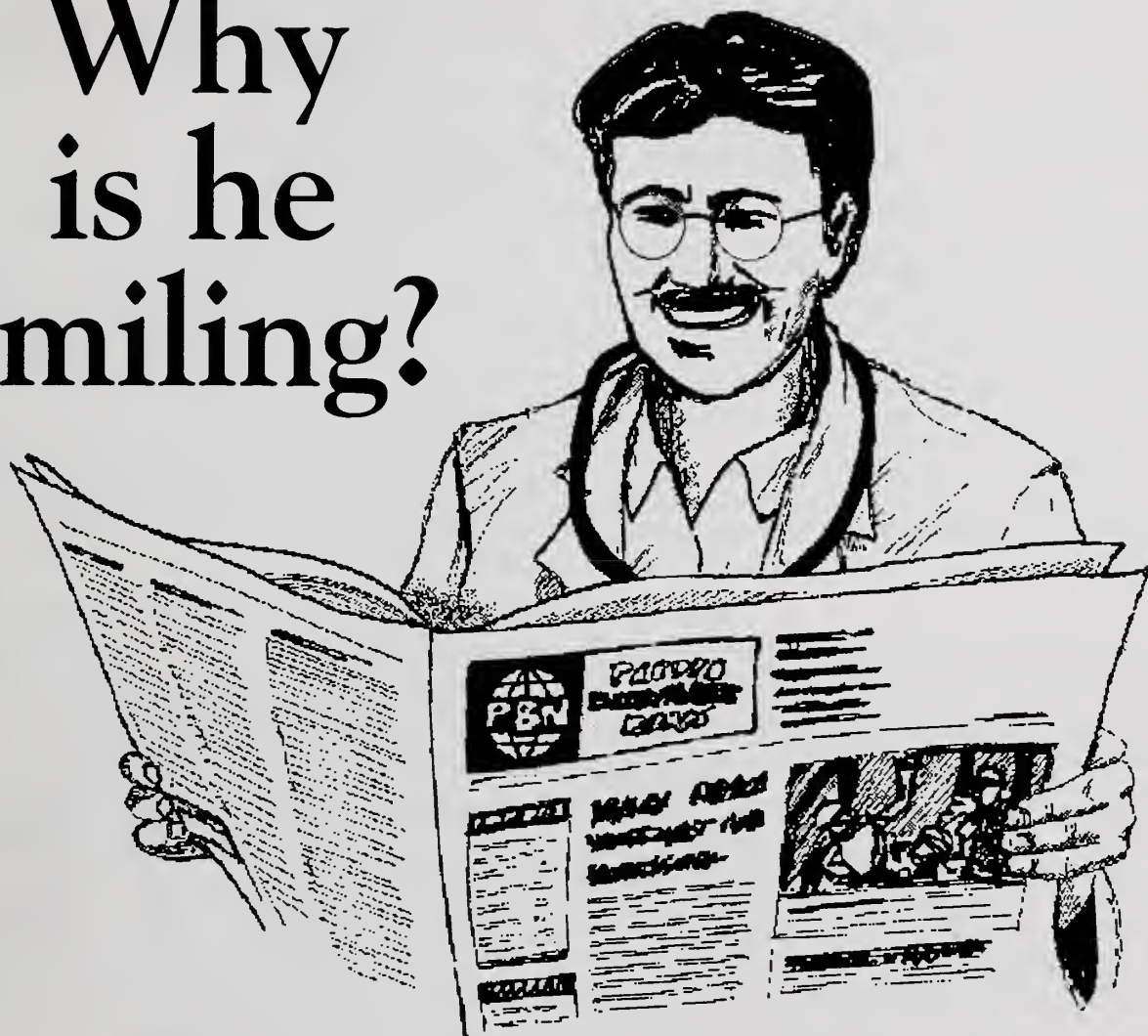
There were 5 cases of uterine scar separation in the 483 women who underwent a trial of labor after previous C-section resulting in an incidence of 1.04%. During this same time period, 265 women underwent routine repeat cesarean section with one case of scar separation resulting in an incidence of 0.38%.

There were 5 infants out of the 483 cases of VBAC with an Apgar score of ≤ 6 at 5 minutes, resulting in a perinatal morbidity rate of 1.04%. One case was due to fetal distress, and

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the other 4 were due to intrauterine fetal demise resulting from 2 cases of *abruptio placentae*, one cord accident and one trisomy.

There were 3 sets of twins in the VBAC group in this study (Table 3). All 3 were vertex/vertex presentations and were delivered vaginally with excellent maternal and neonatal outcomes.

Three patients were delivered by breech extraction in the VBAC group (Table 4); birth-weights ranged from 1905 to 3274 grams. Two had vaginal deliveries with excellent outcomes; the third was stillborn secondary to trisomy 18. There were no maternal complications in the 3 cases.

There were 2 cases of VBAC with shoulder dystocia (Table 5). One infant had a birth-weight of 3980 grams and there were no complications. The other case had an infant weighing 3805 grams which resulted in a uterine dehiscence that did not require repair. Both infants had good neonatal outcomes.

Forty-seven patients with prior cesareans required induction of labor with Oxytocin; of these, 30 (63.8%) had successful VBAC.

Discussion

Since the American College of Obstetricians and Gynecologists published its first set of guidelines in 1982 for vaginal birth after C-section (VBAC), the incidence of trial of labor in patients with a scarred uterus has increased dramatically⁸. The trial-of-labor rate of 65% reported here is at the higher end of the range of 36% to 66% reported in other VBAC studies^{4,8,9}.

A survey by Shiono et al in 1987¹⁰ showed that 92% of women with a history of previous C-section were delivered by elective, repeat cesarean. In addition, 54% of the nation's hospitals had never attempted VBAC at that time⁴.

As a teaching hospital, KMCWC has 24-hour, in-house physician coverage and encourages VBAC candidates to attempt a trial of labor if no absolute contraindications exist. The successful VBAC rate at our institution of 73.7% is comparable to the national range of 54% to 89%². The majority of unsuccessful cases (76%) was secondary to failure of progression in labor. This is consistent with other VBAC studies which also find this to be the most common cause of failed VBAC^{2,8}.

Our study looked at potential complications of vaginal birth after cesarean. One of the potential complications is significant perineal laceration. A study by Yetman and Nolan in 1989 showed that the incidence of significant perineal lacerations, including a "third-degree" tear (complete disruption of the rectal sphincter with intact rectal mucosa), "fourth-degree" tear (disruption of the rectal mucosa and the sphincter muscle) were significantly higher in VBAC deliveries⁹. Yetman and Nolan observed a 31% laceration rate in normal VBAC deliveries and a 56% laceration rate in operative VBAC deliveries. Our study reports a 6.2% and 14.6% laceration rate for normal and operative VBACs respectively. This is considerably less than Yetman's study. In addition, our rates of perineal lacerations also are less than those of Yetman's control population of patients without prior cesarean (19% for NSDs and 49% for operative vaginal deliveries).

Another complication of VBAC is uterine scar separation. Most large-scale studies of VBAC have found the incidence of

Table 1. Vaginal birth after Cesarean section (VBAC) January 1990 to July 1991 (19 months)

Total previous C-section (C/S) patients	748
Patients electing trial of labor	483 (64.6%)
Successful vaginal delivery in trial of labor patients	356 (73.7%)

Table 2. Indications for repeat C-section in patients who elected a trial of labor after previous C/S

Indication	patients	%
Failure to progress	96	76
Fetal distress	26	20.5
Cord prolapse	3	2
Pre-eclampsia	2	1.5
Total	122	100

Table 3. VBAC-Twin Deliveries January 1990 to July 1991

Presentation	Weight in g	Apgar @ 5 min	Prior C/S Indication
Vtx/Vtx	3095/2560	9/9	Failure to progress
Vtx/Vtx	2735/2700	9/7	Breech
Vtx/Vtx	3095/3065	8/9	Fetal distress

Table 4. VBAC - Breech Deliveries January 1990 to July 1991

Weight in g	Apgar @ 5 min	Prior vaginal delivery
3274	8/9	Yes
2240	8/9	Yes
1905	0/0	No

Table 5. VBAC - Shoulder Dystocia January 1990 to July 1991

Prior C/S Indication	Weight in g	Apgar @ 5 min	Complication
Face presentation	3805	7/9	Uterine dehiscence
Failure to progress	3980	3/8	None

(Continued on page 42) ►

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9:00-10:00 am	Kenneth Pruett, M.D. University of Hawaii "Current Research and Advances in Estrogen Replacement Therapy"
10:00-11:00 am	Richard D. Wasnich, M.D., F.A.C.P. Director of The Hawaii Osteoporosis Center "Appropriate Selection of Women for Osteoporosis Prevention Therapy"
11:15-12:00 am	George Burnell, M.D. Chief of Psychiatry, Kaiser Permanente "Psychosexual Medicine in Mid-life"
12:00-12:45 pm	Douglas Soderdahl, M.D. The Honolulu Medical Group "Issues In The Aging Male"
12:45-2:00 am	Complimentary Lunch Keynote Speaker Malcolm Carruthers, M.D., F.R.C.Path. Director of The Hormonal Healthcare Centre, London "The Viropause and Male Hormone Replacement Therapy"
2:00-3:00 pm	Michael Hansen, M.D. Director of The Moller Clinic, Copenhagen "Testosterone Treatment of Cardiovascular Diseases"
3:00-4:00 pm	Open Forum on Hormone Replacement Therapy

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scar separation to be between 0.50% and 2.23%⁹. The outcomes of scar separation range from asymptomatic, found on manual exploration, to catastrophic with fetal distress and hemorrhage requiring hysterectomy. As surveyed by Flamm et al, there have been no American reports of a perinatal or maternal loss attributable to complete rupture or dehiscence of a lower uterine segment scar⁴. Our data, January 1990 to July 1991, show a scar-separation rate in patients with a trial of labor after previous cesarean delivery of 1.04%. However, routine manual exploration of the lower uterine scar was not mandatory in this study and asymptomatic separations may have gone undetected. This is compared to the scar-separation rate of 0.38% in patients who elected to have a repeat cesarean section. Prior studies have not found statistical significance between groups undergoing a trial of labor and those having repeat C-sections². The latest report of maternal mortality published by the State Department of Health in 1989 shows that cesarean delivery still carries a 3-fold risk of mortality compared to vaginal delivery.

Another potential complication of VBAC is fetal morbidity and mortality. No delivery route is free of risk to the fetus. However, it has been shown that when iatrogenic prematurity is eliminated, respiratory morbidity, regardless of gestational age, is higher in pregnancies that are delivered abdominally than in the absence of labor³. Examination of Apgar scores after a VBAC attempt reveals that 5 infants out of 483 (1.04%) VBAC births had an Apgar score of ≤ 6 at 5 minutes. This is comparable to other VBAC study rates that range from 1.79% to 3.90%⁹. The perinatal mortality rate in this study population was 8.3/1000. This is comparably less than the rate of 18/1000 reported for a trial of labor in a meta-analysis review of 10 studies that included over 4500 births¹. In addition, our rate was less than their reported perinatal mortality rate of 10/1000 births for elective repeat C-section.

Twins, which occur in approximately 1% of all pregnancies, represent a small but significant group of patients who might be considered candidates for a trial of labor after prior cesarean delivery. In a 1989 study by Strong and Phelan, 72% of patients with twin gestation who underwent a trial of labor were delivered vaginally of both infants. The study showed that unlike singleton pregnancies, successful vaginal delivery rates for twins appear to be unrelated to the reason for primary C-section¹². In addition, there were no significant differences in maternal or neonatal morbidity or mortality rates in any comparison of trial of labor versus no trial of labor including Apgar scores, birth trauma, neonatal death, birth weight, uterine dehiscence or hysterectomy rates. At our institution, 3 patients with twins underwent a trial of labor and were all delivered vaginally and successfully. All 3 sets were vertex/vertex presentation and had excellent maternal and neonatal outcomes.

Approximately 100,000 cesareans are performed yearly for breech presentation to avoid the complications associated with a vaginal breech delivery, including arrest of the aftercoming head and brachial plexus injury. Therefore, there is very little data regarding outcomes of the breech VBAC infant. However, Sarno and Phelan performed a prospective study on 27 patients with breech presentation and a prior C-section. Their study showed that 50% of patients with a trial of labor for breech with a prior C-section can be expected to be delivered without an

increase in fetal or maternal morbidity or mortality. At KMCWC, 3 patients with a breech presentation underwent a trial of labor. All 3 were delivered vaginally. One case was an intrauterine fetal demise secondary to trisomy 18; labor was induced. The other 2 cases had good neonatal outcomes; there were no maternal complications. It is obvious that more study is needed in this area.

ACOG guidelines currently hold that Oxytocin administration during an attempted VBAC remains controversial. However, several studies have shown that the use of Oxytocin for induction or augmentation of labor in gravidas with prior lower segment deliveries have approximately a 63% chance of successful VBAC¹.

In addition, studies show no increased risk of uterine dehiscence or rupture, need for transfusion, birth trauma, or adverse maternal or neonatal outcome. At our institution, 63.8% of patients whose labor was induced had successful VBAC, compared to 73.7% who were delivered vaginally without Oxytocin. Our rates are comparable to those in other large-scale studies.

Summary

This study confirms that trial of labor for vaginal birth after C-section is well established at Kapiolani Medical Center for Women and Children in Honolulu, Hawaii, for routine pregnancies, with an excellent chance of success and with low rates of complication in both mother and infant. In addition, as research and technology broadens, trial of labor may become more common; in the less ordinary obstetrical cases, the presence of a perinatologist is helpful.

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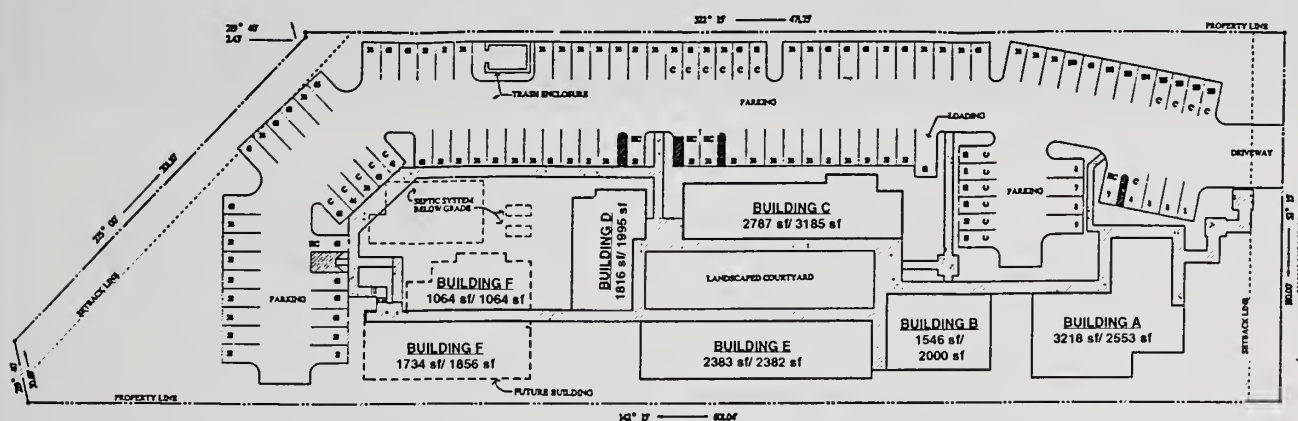
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Cross-cultural Dream Use in Hawaii

J F Pagel MS/MD*

B H Vann PhD**

Cultural variations in the narrative content of dreams have been reported in many studies^{1,2}. This basic cultural difference in dream language and representations has been used to support psychoanalytic theories of dreaming, especially that of the Jungian-based schools^{3,4}. Others have postulated that such variations reflect the cultural differences that each individual experiences during waking life. This "continuity" hypothesis proposes that a high correlation exists between an individual's waking life and his or her dream content^{5,6}.

The biologic framework of dreams, sleep/dream-state physiology, is cross-culturally consistent, and the incidence of dream related pathology also is remarkably similar between differing cultures^{7,8}.

Recent research suggests that significant age and gender variations exist in another dream-related variable, dream use, which is defined as the incorporation of dream mentation into waking behavior⁹. Our study attempts to document whether variations in reported dream use occur in an ethnically heterogeneous Hawaiian population. It is postulated that cross-cultural variations in reported dream use would occur if incorporation of dreams into waking life is culturally learned behavior.

Methodology

A questionnaire on dream use was distributed in the waiting room of a family practice medical clinic in Eleele, Kauai, Hawaii, over a 2-month period. Of 280 forms distributed, only those including appropriate demographic data were retained for analysis. Three questionnaires were excluded because the respondents did not remember their dreams.

The final sample consisted of 265 completed questionnaires. The average age of respondents was 37.9 years. Twenty-seven percent were men (N=72) and 72% were women (N=192). There was no significant age difference between the 2 sexes.

The questionnaire consisted of 23 questions designed to assess the effect of dreams on waking behavior and whether dreams caused stress. The response categories were in Likert-scale format and were coded for analysis into 6 graduated categories from 0=never to 5=always.

Factor analysis, a statistical technique used to identify a relatively small number of factors that can be used to represent relationships among sets of interrelated variables, was performed on the dream-use items and the stress-associated items. Composite measures (DREAMUSE and STRESCOR) resulted from this analysis.

Questionnaire responses were analyzed using the Statistical Package for the Social Sciences (SpSSx). Chi-square, t-test and Pearson correlation techniques were utilized to determine the associations between gender, age, race and the dream-use variables.

Results

The statistical evaluation of responses to individual dream remembering and dream-use items (Table 1) revealed that significant age and sex variation occurred. However, no significant cross-cultural variation was found in dream remembering, incidence of dream description to others, or to any of the questions designed to assess the affects of dream mentation on waking behavior. This result was found to be consistent for age- and sex-matched samples. Evaluation of the composite variables, DREAMUSE and STRESCOR (Table 2), also showed no significant ethnic variability.

Discussion

In our study of reported dream use in a heterogeneous Hawaiian population, no significant ethnic variation was found for dream remembering, dream description to others, dream use, or dream association with stressful life events. These findings suggest that the significant gender and age variations in reported dream use do not reflect culturally learned differences in attitudes toward dreams and dream use.


(Tables continued on page 46) ►

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Table 1. Pearson Correlation Coefficients Showing Association between Age, Sex, Race, and Dream Utilization

	AGE	SEX	RACE	REMEM	DESCR	ACTIV	OTHS	SELF	WORK	EMOT	REL	DEC
AGE	1.00											
SEX	-.01	1.00										
RACE	-.06	.17***	1.00									
REMEM	-.15*	.12*	-.00	1.00								
DESCR	-.14	.24***	.05	.40***	1.00							
ACTIV	-.23***	.12*	.04	.21***	.33***	1.00						
OTHS	-.24***	.14*	.07	.27***	.28***	.36***	1.00					
SELF	-.17**	.15**	.03	.23***	.32***	.40***	.54***	1.00				
WORK	-.15**	.10	-.03	.12*	.17**	.37***	.46***	.52***	1.00			
EMOT	-.24***	.19**	-.02	.32***	.29***	.41***	.50***	.60***	.57***	1.00		
RELA	-.23***	.15**	.01	.31***	.29***	.35***	.56***	.53***	.53***	.68***	1.00	
DEC	-.25***	.13*	-.01	.17**	.25***	.36***	.47***	.40***	.35***	.44***	.48***	1.00

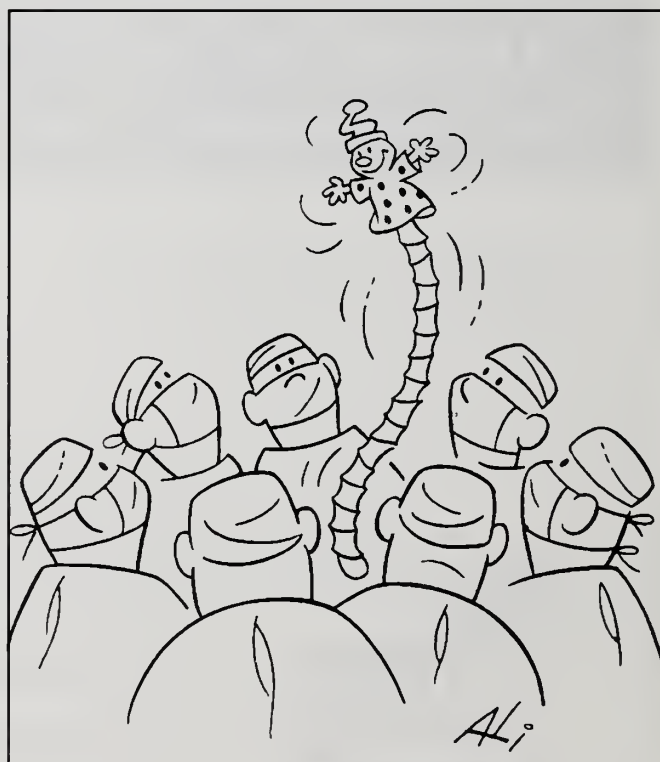
*p<.05 **p<.01 ***p<.001

KEY- REMEM - Remembers dreams
DESCR - Describes dreams to others
ACTIV - Uses dreams in daily activities
OTHS - Dreams affect attitudes toward others
SELF - Dreams affect attitudes toward self

WORK - Uses dream in work
EMOT - Dreams affect emotions
RELA - Dreams affect relationships
DEC - Uses dreams in making decisions

Table 2. Mean Values of Composity Variables DREAMUSE and STRESCOR, by Race

DREAMUSE Race	Mean	SD	N
Caucasian	10.5	3.3	44
Filipino	10.6	3.4	79
Japanese	9.4	3.0	39
Asian	10.0	2.7	11
Hawaiian	10.9	2.7	29
STRESCOR Race	Mean	SD	N
Caucasian	10.2	2.6	46
Filipino	9.8	2.8	77
Japanese	8.5	2.3	38
Asian	9.5	2.1	11
Hawaiian	10.2	3.1	28





Henry N Yokoyama MD

Personalities

Donald Pachuta, internist and infectious disease specialist, is the newest member of the Kauai Medical Group. Donald has traveled the U.S. since 1983 advocating "living long and living well with AIDS and HIV". In 1990, he edited a landmark special issue of the *Maryland Medical Journal* dedicated to the idea of living long and well with AIDS. Donald is a pioneer in the field of guided imagery for the treatment of life-threatening diseases and has traveled throughout the U.S. and Europe as a Marquette University lecturer. He has co-edited a 400-page book on the mastery of stress, health and well-being called *The Life You Save May Be Your Own*. Another special interest is oriental medicine and philosophy and the integration of eastern and western approaches to illness.

Oncologist Reginald Ho, our newly elected president of the American Cancer Society nearly went into the seminary instead of medical school. Reggie says: "If someone wants to go into oncology, I'd like to see a bit of a priest in him or her."

Personable Amelia Jacang, a practicing pediatrician, Aloha Medical Mission volunteer, and mother of 3 boys, has been working on a Filipina Women's League cookbook. She has appeared on the live TV program "Hari's Kitchen" to demonstrate Filipina cooking.

Excerpts from *Stitches*, (the Journal of Medical Humor) Premiere Issue Fall 1992

"Trial By Laughter" by Peter MacDonald, a lawyer who collects and publishes funny legal stories.

Q. And, Doctor, as a result of your examination of the plaintiff, was the young lady pregnant?

A. The young lady was pregnant, but not as a result of my examination.
(Like anyone else, lawyers sometimes let their syntax get out of whack.)

Q. Doctor, what treatment did you give this man?

A. I cleaned the wound, sutured it and put him to bed with a nurse.
(Sometimes a witness knows what he wants to say, but when he opens his mouth the wrong words come tumbling out.)

Q. Do you think this is a permanent condition, Doctor?

A. Well, it's temporarily permanent.

(The verbal carnage continues. Consider this, from an auto accident case:)

Q. Now, Mrs Smith, have you ever had any other accidents?

A. No, but I had a baby once.

(A woman was describing a fight in which she was injured when the judge asked the question:)

Q. Were you kicked in the fracas?

A. No, your honor. I was kicked about halfway between the fracas and the belly button.

Oncology Dialogue

A 61-year-old woman with intermittent obstipation for 4 or 5 years had negative BE studies. She was lost to follow-up for 2 years and presented 1 month ago with bloating and intermittent loose stools. Her PMD sent her to a gastroenterologist who found a rectal mass 2 cm from the anal verge. She had an exploratory laparotomy and the rectal tumor was excised. The surgeon felt an area of density in the liver. Preop CEA was 6.6. Radiologist Howard Arimoto reviewed the CT scans which showed suspicious perirectal adenopathy. The CT scan of the liver showed 2 areas of either tumor or cyst. An ultrasound leaned more toward an hemangioma of the Rt lobe. Pathologist Larry McCarthy reported the rectal tumor measured 4 1/2 x 5 1/2 cm and microscopically showed well-differentiated adeno Ca with invasion of the muscularis mucosa. Two nodes out of 28 harvested were positive.

Moderator Ken Sumida asked, "How do we follow the patient?" Surgeon Scott Hundahl suggested, "We follow with CEAs. It takes 6 to 8 weeks after surgery for the CEA level to come down." Ken turned to pathologist Grant Stemmerman and inquired, "What are the risk factors for rectal CA?" Stemmy summarized: "Until 1960, 70% were within 6 cm of the dentate ligament, but with increased risk factors, the CA has become more proximal. Beer drinking is a risk factor. Smoking is not. Calcium deficiency is suspect, eg the higher incidence in Japanese-Americans who ingest less dairy products because of lactose deficiency."

When queried, Cancer Research Center of Hawaii director Brian Issell discussed the various protocols available for colorectal cancer and mentioned the SWOG, a protocol in which the combination of radiation and chemotherapy was important. "She can be placed on Stage 3 or Dukes C protocol."

Stemmy mentioned, "The NSABP study protocol says women will not receive MeCCNU." Scott: "I wondered about that. And most of the studies do not include women." Moderator Ken Sumida adds, "MeCCNU has a high incidence of leukemia. Perhaps that's why." Chemotherapist Dennis Wachi whispered to us, "I saw a patient develop leukemia on MeCCNU. . . I never use it."

More excerpts from *Stitches*

"Special delivery" by Dr Herb Basian

As a resident responsible for the surgical services in the emergency room of a large New York hospital, I was privileged to provide supervision over the interns.

One night, a gentleman in a fedora and a very harried expression burst into the ER shouting, "Help! Help! Hurry! My wife is having her baby in the backseat of the cab!" Our aggressive, eager intern, with his first week's exposure to ER problems, coolly grabbed the emergency pack for ligating umbilical cords, dashed out into the driveway, jumped into the backseat of the cab, which was one of a line of cabs in the usual site, and quickly lifted the hem of the dress of the lady in the backseat and as he groped for the panties, he realized he was in the wrong cab.

So much for the differential diagnosis.

"A mystery solved" by Dr Herman van Norden

I was examining a baby girl a few weeks of age who lay naked on my examining table while her 3-

year-old brother watched intently. The following conversation took place:

I: "Is this a boy or a girl?" Brother: "A girl."
I: "Good. How can you tell?" Brother: "Mamma told me." I: "Very good. But how did Mamma know?" Brother (after some thought): "The people in the hospital told her." I: "Excellent. But how did they know?" Brother (after long thought): "They X-rated her."

"Natural rhythm" by Dr Peter Levers

For some years now, I've been using a standard functional inquiry. One day a very large Swedish gentleman came into the office, and I began to ask him my series of standard questions. When I asked, "Do you have a good appetite?" the answer was, "Ya, my appetite is good." Then I asked, "Do your bowels move?" to which he replied, "Ya, but they sving a bit ven I valk."

The remainder of the examination was conducted with some difficulty.

Oncology Dialogue

A 53-year-old oriental man had a left-leg melanoma excised and several years later developed pleural mets which were again removed. He now presents with brain mets. Someone asked, "Do mets metastasize?" Oncology surgeon Scott Hundahl called on his MD Anderson experience: "Dr Fiddler ground up melanoma mets and inoculated rats. He found that liver mets went to the liver and lung mets went to the lungs . . . The answer is 'Yes, mets do metastasize.'"

The patient had presented with a solitary large hemorrhagic lesion of the occipital lobe. Pathologist Grant Stemmerman reported, "If we had no history on the patient, we would have called the tumor a glioma because melanomas usually metastasize to the frontal lobe with multiple rather than solitary lesion."

Moderator Ken Sumida asked, "How would you handle the case?" Scott, without his usual enthusiasm intoned, "A combined modality is recommended . . . Resection alone has an 85% recurrence rate while resection with radiation has a 21% recurrence." Radiotherapist Lois Mastrofrancesco added, "I offered the patient postop radiation. We have to consider long-term toxicity which depends on fractionation and total dosage. Toxicity includes subtle changes in cognition and memory—sort of a global dysfunction." Ken, who obviously finds brain radiation distasteful: "So a dementia-like picture especially in patients over age 65." Radiotherapist Thanh Huynh discussed the biology of irradiating melanomas. "It was formerly thought that melanomas were resistant to radiation, but we now have learned otherwise. Melanomas have greater 'shoulders' and require larger doses, viz 300 rads rather than the standard 200 rads." Ken commented, "The controversy is that of toxicity versus results." Scott asked the audience, "Does anyone have a case of a 5-year cure after brain radiation?" Someone had one case—the outlook for the patient appeared dismal.

Lecture Notes

"Treatment of Early Breast Ca by Breast Conservations", Lois Mastrofrancesco on July 17, 1992, at QMC Kamehameha Auditorium (Notes therefrom)

Incidence of Breast Ca:

(Continued) ►

- a. Most common cancer in women.
- b. Second most common cancer nationally.
- c. Most common cancer in Hawaii.

TNM Staging:

- T1: Less than 2 cm²;
- T2: 2-5 cm²;
- T3: Greater than 5 cm²;
- T4: Extension to skin and nodes.
- N0: No mets;
- N1: LN mets-Not fixed;
- N2: LN mets-Fixed to adjacent tissue.
- M0: M1.
- Stage I: T1, N0, M0 85% 5-year survival.
- Stage IIA: T1, N1, M0 66% 5-year survival.

Treatment Early Breast Ca:

Surgery (Breast conservation); radiation; drugs.

Lumpectomy (Synonyms):

Tylectomy; partial mastectomy; wide excision with negative margins. (Not equal to: quadrectomy; incisional biopsy).

Goals of Breast Conservation:

- Total excision of local disease.
- Negative margins.
- Good cosmetic effect.

Primary Radiation Therapy:

- Local control of primary site.
- Eradication of micro-foci of disease.
- Minimal side effects.
- Good cosmetic results.

Typical Course of Radiation Therapy:

- Daily therapy 5 to 7 weeks
- Treatment: whole breast and regional nodes.
- Boost to primary tumor bed.
- Dose homogeneity and Rx reproducibility.

Breast Conservation vs mastectomy (Stage I & II):

- No difference in local mets, disease-free survival and long-term survival.

Patient Selection for Breast Conservation Therapy:

- Any age with newly diagnosed cancer.
- Invasive Ca (ductal, lobular, tubular, colloid).
- Tumor size less than 4 to 5 cm².
- N0 or N1 nodes.

Absolute Contraindications:

- Multifocal disease
- Diffuse micro-calcifications
- Pregnancy
- Prior XRT
- Collagen vascular disease

Relative Contraindications:

- Large breast

- Large tumor/small breast
- Subareolar location
- Psychosocial factors

Possible Contraindications:

- Extremes of age, ie too old or too young.
- Histopathology: Extensive DCIS (ductal Ca in situ).

Information for Patient Selection:

- H&P
- Histopathology
- Mammography
- Appraisal of patient needs

Individualized Therapy after Patient Selection:

- Is re-excision indicated?
- Is boost radiotherapy indicated?
- Is regional node irradiation indicated?

Complications of Treatment:

- Lymphedema
- Lung fibrosis
- Rib fragility
- Second malignancy

70% of Stage I/II breast Ca are cured.

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Maka O Ke Kauka

Russell T Stodd MD

There's no stronger bond of friendship than a mutual enemy.

What a great pleasure to have the outgoing president of the American Academy of Ophthalmology, Froncie Gutman, MD at the November meeting of the HOS. His message was informative and timely, outlining how the AAO and the various local organizations must work together in the challenging days, months and years ahead. Speak loudly and carry a combined, organized, rational, intelligent plan. Additionally, at the December meeting of the AMA House of Delegates, President John Clowe, MD of New York, emphasized forcefully that doctors must speak with one voice. Self-protective agendas of individual medical organizations must be put aside so the AMA, ASIM, ACP, ACS, et al., unite in one voice to protect the freedom of patients and physicians.

The easiest way to make money is to stop losing it.

Henry Hirschman, MD, outspoken California eye surgeon, made a compelling point at a recent conference. He noted that Medicare reimbursement for cataract surgery when performed in a freestanding surgical center is approximately \$1,000 less than the average amount paid for the same procedure accomplished in a hospital setting. Therefore, said Dr. Hirschman, if Medicare would simply level the playing field for hospital reimbursement to equal that afforded surgical centers, Medicare would save approximately \$1 billion, (that's with a B) a year.

First draw your conclusions—then plot the data.

Meanwhile at the opposite pole, government regulators and some insurers are pressing physicians to divest themselves of imaging centers, laboratories, and other medical businesses to which they might refer patients. The claim is that self-referral can lead to overuse of services. The issue continues to be a hot one for the AMA with conflicting policies from the AMA House of Delegates and the AMA Council on Ethical and Judicial Affairs. The issue is one of *patient exploitation* which is obvi-

ously wrong. However, if a crooked doctor chooses to take advantage of his or her patient and/or insurer, he or she will find a way to do so. Burdensome regulations and ethical ostentation regarding labs, pharmacies, joint ventures, and medical equipment will not serve as a deterrent.

If you're already in a hole, why continue digging?

At the direction of the Hawaii Legislature, our governor recently appointed a *blue-ribbon panel* to study the cost of health care and make remedial recommendations. One of the proposals was for a no-fault system of compensation designed to negate the high cost of medical liability insurance and to discourage defensive medical practices. However, several studies have revealed that medical injuries occur at a rate many times the number of complaints. Therefore, a no-fault system, especially one managed by a government agency with taxpayer's dollars, would surely be far more costly than the tort system. Our present medical tort process has major flaws, but a no-fault mechanism is decidedly not the solution.

Medicine around the world—Italy.

Twenty-thousand doctors marched in Rome to protest the loss of their public trough jobs! Why? Because the government, seeking to shrink the swollen budget, would spur more private medical practice and require people with higher incomes to pay for a bigger share of their health care, reduce remaining medical and administrative staffs, and require the units to have a balanced budget. We would pray for such action in America, but our Congress, failing to learn by the errors of Europe, plans just the opposite.

Medicine around the world—Japan

Delivering excellent medical care is not an example of Japanese superiority. Medical care is full of trouble spots—Japanese consume enormous amounts of prescription drugs, highest per capita in the world and over twice that of the U.S. There is a passion for diagnostic tests, Japan has more advanced diagnostic tools (like CT scanners) than any other country.

Unevenly trained physicians own and operate the bulk of "hospitals," some with as few as 20 beds. Public hospitals are prestigious but are incredibly busy with doctors seeing as many as 100 patients in a morning. Forty percent of inpatients are over age 65, half are hospitalized longer than 6 months, and the average length of stay is 40 days! Although health indices are accepted as excellent, most epidemiologists account for Japan's comparative good health as largely the by-product of economic accomplishment—low level of unemployment, a good diet, decent maternal and child care, high level of education, and a relatively equal distribution of income.

It is the will of God that we must have members of congress, missionaries, critics and the IRS, and we must bear them.

As required, a widow filed a tax return for her recently deceased husband. One year later came the IRS reply addressed to the decedent—"We are processing your gift tax return and find we need additional information. Please provide your date of death. We apologize for any inconvenience we may have caused you and thank you for your cooperation." Thanks, S.S. and the *Wall Street Journal*.

Addenda

▲ Penetrating injury resulting from eating utensils contaminated with oral flora caused culture-positive bacterial endophthalmitis in 4 of 6 eyes.

▲ Economy in the doldrums? Not likely. VISA holiday charge purchases were up 16.5% over 1991!

▲ Our national flower should be the concrete cloverleaf.

▲ There's less and less fun in medicine, but there is a lot of medicine in fun.

▲ Why do elephants drink? It helps them forget.

Aloha, and keep the faith.

rts

Classified Notices

To place a Classified Notice:

MEMBERS, please send typewritten ad to HMA office.

NON-MEMBERS, please call Leilani at 521-0021. Four-

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Medical Office Space — Established medical office space to share at 1040 South King Street, Suite 312, Honolulu, Hawaii, 96814. For information, please call 531-8576.

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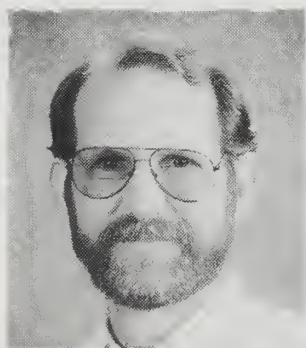
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PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylated metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids (1 hour prior to PRAVACHOL), cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal and/or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a $\geq 50\%$ rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spiroglactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear (Wallerian-like) degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagenesis tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/– mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: **Pregnancy Category X:** See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg/day or in rabbits at doses of up to 50 mg/kg/day. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	4.4	6.9	2.0	3.9
Constipation	5.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

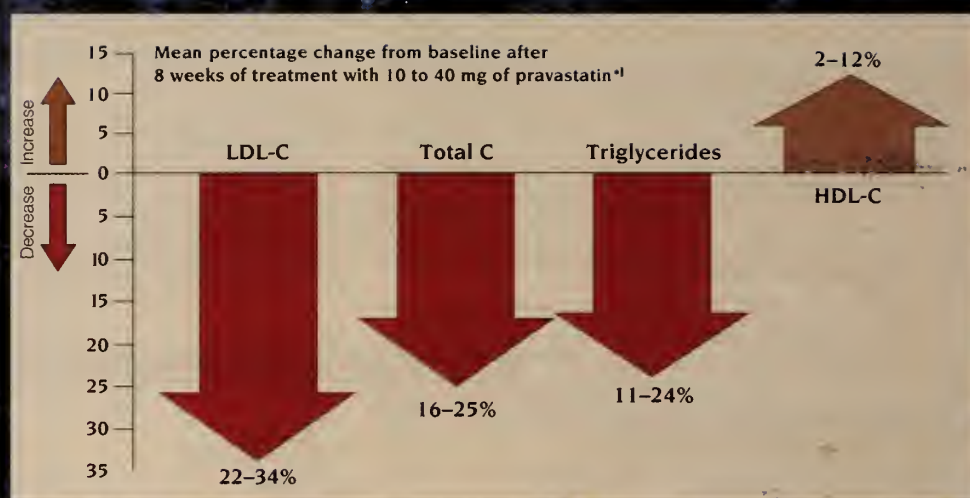
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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

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Hawaii MEDICAL JOURNAL

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Highlights of the HMA Council Meeting

The HMA Council met 5 February 1993. Members present were: J Chang, A Don, F Holshchuh, J Spangler, S Wallach, C Kam, R Stodd, P Blanchette, C Lehman, B Shitamoto, R Lee-Ching, M Cheng, HKW Chinn, P Chinn, P Hellreich, S Hundahl, R Kimura, M Shirasu, C Kadooka, P Kim, J Betwee, R Smith, G Goto, J Lumeng, W Chang, N Winn, A Kunimoto, J McDonnell, WWL Dang, J Armstrong; F Reppun, Editor, *HMJ*; HMA Public Relations Committee Chair S Levine; Legal Counsel Vernon Woo; Auxiliary representative Maureen Lau; HMA Staff: J Won, B Kendro, L Tong, J Asato, J Estioko, P Kawamoto and A Rogness (recording secretary).

The Council heard a report from Ms. Winifred Odo, Medicaid Program, regarding efforts to stem the mounting program deficit of another \$48 million and possible solutions including more restrictions on eligibility, deletions in optional benefits such as podiatry, and required generic prescribing.

Treasurer John Spangler reported the HMA will not experience a deficit for 1992.

The HMA Auxiliary reported on its projected May 23, 1993, fashion show at the Sheraton Waikiki with loads of physician models as well as spouses and pleas for physicians to buy tickets to benefit the Waianae Coast Comprehensive

Health Center Scholarship Fund for health care education.

The Council approved an HMA television show to appear on public broadcast station KHET featuring a live talk show with dialogue on health issues. The PR Cmte will raise \$80,000 funding, which the chair of the HMA Public Relations Committee, Steve Levine, has already begun.

It approved working with Neighbor Island medical societies to seek true autonomy for county/state hospital operations at appropriate levels for each county.

Support was reaffirmed of involuntary HIV testing when a health-care worker is injured and the patient refuses consent, but the patient's blood is already available.

A ban of fireworks for personal use was endorsed with an allowance for public display of fireworks.

Council supported legislation to fund a family practice residency program in Hilo.

The HMA Distinguished Medical Reporting Awards banquet is to be held on April 24, 1993, with a roast of Mayor Frank Fasi and confirmed roasters will include Larry Price, Frank DeLima, Danny Kaleikini, Karen Keawehawaii, Michael Qseng and Mufi Hanneman. Call HMA office for information about buying tickets.

Fred Holschuh
Secretary



Rx Privileges for Advanced RN Practitioners

Members of HMA may remember, if they were present at the 136th annual meeting of the House of Delegates last October at the Ilikai Hotel in Waikiki, or if they read the highlights of that session in the *Journal* in its November 1992 issue, that the House voted to refer the 3 resolutions 8, 11 and 13 related to nurses prescribing medications, to the Council in order for it to come up with a policy statement.

President Jeanette Chang then appointed an ad hoc committee that was to meet with the nurses in order to discuss the issue; she appointed Patricia Chinn to be the committee's chair.

The issue had arisen previously when the nurses had attempted to prevail upon the State Legislature to enact a bill that would allow advanced practice nurses to prescribe independently from a formulary. This the HMA opposed and the Legislature turned down. However, the nurses are trying again to introduce a similar bill this year.

The HMA's position had been to oppose prescribing by advance practice nurses.

The committee again met to discuss the issue on January 8. The discussion on the issue was free and prolonged. There were strong arguments made pro and con, the most telling of which was that an HMA survey last year indicated a majority of its members did not favor granting the privilege. The Committee passed the motion to deny nurses that privilege by a wide margin. It was also

revealed to the Committee that the Legislators were not willing to consider the bill until they could be assured that the doctors and nurses had come to an agreement as to when the bill should be presented.

At the Council meeting that followed immediately, Pat Chinn gave the report of the committee's action, and it was accepted as a motion requiring no second. Again there was considerable discussion; when it came to a vote, the motion failed to pass by a narrow margin.

A new motion was introduced, seconded and passed unanimously. It was stated as follows:

"The HMA opposes any nurse prescriptive authority legislation that compromises the public safety and its quality of medical care, which is what has been presented thus far [by the nurses]. The HMA has always been open to, and continues to be open to, discussions for proper and appropriate legislation in this area."

The Council of the HMA has spoken with one voice. The Council was authorized by the House of Delegates to do so. The statement above is now the policy of the HMA. It reflects the majority vote of the HMA membership as well.

We respect the feelings of the ARNPs in wanting to do what they feel they are capable of doing: To diagnose and treat the common, simple ailments of the general public, particularly in situations where physicians may be scarce or overwhelmed by the number of people seeking access to their services. It is not intended

(Continued on page 58) ►

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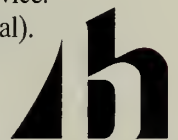
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to denigrate the role of the nurse specialists who have undergone extensive training and who develop a considerable experience. However, not only is the practice of medicine by physicians now fraught with hazard— (a) that diagnosing what seems to be the onset of a benign illness only to see the patient get seriously worse with a possible life-threatening outcome (granted that ARNPs may be even quicker to seek consultation than physicians); (b) that the incidence of iatrogenic illness is much higher than it ever was in the past because we now have such a large armamentarium of highly potent drugs (a cram course in pharmacology even up to a year, much less 30 or 90 days, is totally inadequate); (c) that sometimes even the most innocuous of medicines can cause severe reaction; and (d) that physicians have a sometimes overwhelming burden of responsibility and liability; we do not quite understand why nurses aspire to assume the role of independent practitioners.

We feel that if a qualified nurse aspires to the role of a physician, she or he should consider becoming a full-fledged doctor of medicine.

This is not a battle for turf; God knows we physicians could do with more help, more time, and fewer patients! Interns and Residents already have their degrees in medicine; they also are licensed to practice, but with strict limitations, the chief one of which is "under supervision and in an institutional milieu".

We physicians welcome close collaboration with our assistants, be they nurses, PAs or other assistants, but we believe that the people who seek access to medical care will sometimes not be well-attended by a practitioner who acts as a physician, but is only half-trained to be one. The usual, gullible patient can hardly ever tell the difference (especially now that we professionals—doctors and nurses—so often no longer wear distinctive uniforms!).

In short, we think the HMA has carefully considered the issue and has come up with a reasonable policy. It is now up to the nurses; the ball is in their court.

J I Frederick Reppun MD
Editor

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I certify that the statements made by me above are correct and complete. (HMJ 3/93)
STEPHEN S. LENT, Publisher



A tropical disease

We are delighted to be able to publish a case report coming out of the Waianae Coast Comprehensive Health Center.

Cedric Yoshimoto MD not only provides us with an interesting reading of a case with dermatological complaint, but he also astutely has made the correct diagnosis based on a high index of suspicion (after all, we haven't all gone to the school of tropical medicine in London, as has Cedric!). What's more, as a family physician, Cedric is to be commended for doing the research as exemplified by the extensive bibliography at the end of his article.

The WCCHC is just one of several primary health clinics that are filling a need in our State, particularly geared to providing access to medical care for the poor, the uninsured and the underinsured. These people are the target of Hawaii's unique SHIP—State Health Insurance Program—that has caught the attention of our nation (NBC-TV has recently sent a team to Hawaii to focus on our health care system, to be aired on NBC's "Today" show, Monday mornings from 0700 to 0800— this one on 18 November '92). Hawaii's estimated 30,000 people in this category of the underserved are a part of the nation's 37 million or so. As we were informed at the October '91 HMA annual meeting, SHIP has already accepted more than 16,000 of them. These are the ones not eligible for Medicaid under the State's Department of Human Services; those on Medicaid also have limited access to the services of Hawaii's physicians because, in general, physicians have difficulty caring for patients for a fee discounted well below the physician's overhead expense.

The other subsidized primary health clinics are the Queen Emma Clinics, the Waikiki Health Center, the Kalihi-Palama Health Clinic, Kokua Kalihi Valley Comprehensive Family Services dedicated to the memory of Charlie Judd, the Waimanalo Health Center, the Hilo Bay Clinic and the Pahoia Family Health Center, recently opened on the Big Island.

Readers might be interested to know there is an overall organization called the Hawaii State Primary Care Association, with a board made up of a representative from each of the aforementioned primary care centers that have boards of their own. Larry Muike MD attends the HSCPA, representing the native Hawaiian *Papa Ola Lokahi*, mandated by an Act of Congress to establish 9 health care centers throughout the islands, for the benefit of native Hawaiians.

J I Frederick Reppun MD
Editor

Erratum

We stand corrected for improperly citing what should have been **Igaku Hakase** rather than what we had in the editorial "Sensei" about Dr Ilza Veith: **Itagaku Hase** in the November 1992 issue. The former was the Japanese medical degree she was awarded by the Juntendo University School of Medicine.

The Editor

Strongyloides Infection in Hawaii: An Imported Case

Cedric M Yoshimoto MD, DTM&H*

Tropical diseases may present anywhere in the world. A case of strongyloidiasis in Hawaii, identified by a characteristic manifestation, larva currens, is described. Strongyloides infection may persist long after leaving an endemic area through the mechanism of autoinfection and, especially under circumstances of immunosuppression, may become overwhelming (the hyperinfection syndrome), with a likelihood of being fatal. Each case of Strongyloides infection should be treated aggressively in order to prevent this dangerous outcome; in addition, the parasite should be eliminated before immunosuppressive therapy is begun.

Introduction

Strongyloides stercoralis, the threadworm, is a nematode widely distributed in the tropics and subtropics, particularly in Southeast Asia, tropical South America and sub-Saharan Africa^{1,2}. It also is present in the southeastern United States^{2,3}. This human parasite has a rather complicated life cycle that sometimes results in autoinfection. In such instances, the adult female worm lays eggs that hatch into *rhabditiform larvae*, which in turn develop into invasive *filariform larvae* (a) either within the intestinal lumen or (b) through the perianal skin^{4,5}. In either case, invasion by these larvae through the mucosa or the skin maintains or amplifies the infection in the absence of reexposure to *Strongyloides* from the external environment. In this way, people with the disease may present themselves for treatment far from endemic areas of infection.

Here we have a case to report from the Waianae Coast Comprehensive Health Center.

Case Report

A 45-year-old Vietnamese man presented himself with a complaint of pruritic rash which had reoccurred almost monthly for the past 6 years. He had been treated for this several times previously with various medications, the names of which he did not recall, but with no relief. He reported occasional cough and shortness of breath but no wheezing, abdominal pain or diarrhea. He had lived in Vietnam until 1985, and subsequently had lived in Hong Kong for one year (when the rash first appeared), the Philippines for 6 months, and Kansas for 2 years before coming to Hawaii 2 years ago.

Examination of the skin revealed 3 separate areas (left lower chest, right abdomen, right buttock) of eruption characterized by one or more serpiginous, linear, non-indurated wheals surrounded by an erythematous flare (see Figure). The remainder of the examination was not noncontributory.

Microscopic examination of a stool specimen demonstrated *rhabditiform larvae* of *Strongyloides stercoralis* and hookworm ova.

The patient was given thiabendazole 20 mg/kg p.o. b.i.d. for 2 days and diphenhydramine 25 mg to 50 mg p.o. q.6 h. p.r.n. for the infection and for symptomatic relief of the pruritis respectively. Subsequently he was prescribed mebendazole 100 mg p.o. b.i.d. for 3 days to eliminate the infestation with hookworm.

During the following 4 months he had no recurrence of the rash; this represents the longest asymptomatic period since his affliction began. However, he failed repeatedly to provide a sample for follow-up stool examinations.

Eight family members also lived in Vietnam and were asked to provide stool samples for examination. Only one of them provided a single specimen, which was negative for *Strongyloides*.

Discussion

Uncomplicated *Strongyloides* infection is characterized most frequently by diarrhea and abdominal pain; or it can be totally asymptomatic^{6,7,8}.

In the case we present here, we presume that the patient acquired his infection in Vietnam and that it persisted through the mechanism of autoinfection.

Strongyloides is known to be widespread in Southeast Asia^{1,2}. A high proportion of British troops who served there during World War II and were imprisoned by the Japanese became infected^{9,10,11}, as did some American troops who served in the Vietnam war^{12,13}. Southeast Asian refugees who emigrated to the United States and other countries have shown various rates of infection^{2,14}.

Autoinfection may result in repeated episodes of linear urticarial cutaneous eruptions from migrating larvae, as seen in the present case. This manifestation has been termed *larva currens* (Latin: racing larva) to describe the celerity with which the larvae and consequent rash move and spread, as much as 10 cm per hour¹⁵. This is in contrast to the more deliberate pace of cutaneous *larva migrans*, which is usually caused by nonhuman hookworm larvae, and consists of an indurated linear track with little or no flare¹. *Larva currens* has been described as occurring frequently among the Allied troops who had been prisoners of war in Southeast Asia during World War II^{9,10,11,16,17}. The rash is considered by some to be pathognomonic of strongyloidiasis^{5,9,15}. *Larva currens* is reported infrequently in other areas where *Strongyloides* infestation is endemic; it may be specific to the strain of parasite

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DTM&H is a British degree, signifying Diploma in
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Submitted for publication November 5, 1991.

(Continued on page 61) ►



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prevalent in Southeast Asia¹⁷.

Another consequence of autoinfection is that successive generations of parasites may sustain an infection for an extraordinary span of time. The author saw a patient in London, a former prisoner of war, who had *larva currens* for a period of about 45 years since his repatriation from Southeast Asia. Leighton and MacSween have reported a woman who suffered symptoms of strongyloidiasis for approximately 65 years¹⁸.

A third possible sequelum of autoinfection is disseminated strongyloidiasis, a so-called hyperinfection^{7,19,20}, which may occur in both immunocompetent and immunocompromised hosts. *Filariform larvae* may invade virtually every tissue, sometimes in overwhelming numbers, leading to complications such as bowel necrosis and perforation, pulmonary consolidation, respiratory distress, and bacterial infections (sepsis and meningitis); the latter condition presumably the result of intestinal bacteria accompanying the migrating larvae^{5,6,20}.

The case fatality rate for reported hyperinfection syndrome (HS) is very high, about 77% in immunocompromised hosts according to one review of the English language literature²⁰. Conditions associated with HS include malnutrition⁷, malignancy, particularly of the lymphatic system^{20,21}, and with treatment of corticosteroids or other immunosuppressive drugs^{20,22}. HS has been in patients with the acquired immunodeficiency syndrome^{23,24}, although not to a marked degree²⁵. Of note, the urticaria and pruritis of *larva currens* may prompt treatment with corticosteroids^{8,18}, a potentially fatal error.

The diagnosis of parasitic infections is best accomplished by finding the parasite. Stool examination, as in this case, may reveal *Strongyloides larvae*²⁶. However, larval passage in stools is variable⁶ and multiple examinations may be required⁹. Examination of duodenal contents either by aspiration²⁷ or by sampling with a retrievable swallowed nylon string (Entero-Test, HDC Corp., Mountain View, California) has been advocated²⁸, as has sputum examination for larvae⁵. Pelletier and colleagues have evaluated an ELISA for antibody to *Strongyloides* larval antigen and found it useful¹⁷.

Treatment of uncomplicated strongyloidiasis involves thiabendazole^{29,30}, albendazole, or ivermectin^{30,31}.

In view of the possibility of subsequent HS, every patient in whom *Strongyloides* infection is diagnosed should be treated. Furthermore, every patient in whom immunosuppressive therapy is contemplated, and who may have been exposed to *Strongyloides* eg residence in an endemic area), should be evaluated for the parasite and treated if infected^{2,5,6,9,20,21,22}.

Conclusions

Whether the world is growing smaller (improved communications and transportation, increased travel and migration) or becoming more tropical (global warming), tropical diseases are now a matter of potential concern in every part of the world³². It is being recognized more and more that physicians need to become familiar with this branch of medicine^{33,34,35,36}. For example, the United States, including Hawaii, has recently experienced cases of cholera^{37,38}, malaria^{39,40} and dengue⁴¹ reported from several states. Hawaii is the most nearly tropical of the states and it is a crossroad of Pacific travel. The medical community can expect to encounter a variety of imported, as well as indigenous exotic disorders, and should remain alert to them.



Larva currens: eruption on left lower chest, with several serpiginous linear wheals and surrounding erythematous flare.

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A Rare Case Of Cholera In Hawaii

Gregg M Yamada MD*

Cholera is the most fatal of the infectious diarrheas but only rarely encountered in Hawaii. Two cases previously have been documented in the Islands. We describe an elderly patient, without obvious risk factors, who contracted cholera. Early consideration of cholera as a diagnostic possibility is recommended in patients with unexplained, profuse diarrhea. The unique features of this case are discussed in this report.

Case Report

A 77-year-old Japanese man was admitted to a community hospital for weakness and diarrhea. Four days prior to admission he had a sudden onset of loose, watery stools, but denied any other symptoms. Over the next 2 days, the severity of the diarrhea increased progressively and the patient sought medical attention. He was prescribed an antidiarrheal agent with minimal relief. The morning of admission, the volume and frequency of diarrhea had increased dramatically to 15 episodes per hour; this was associated with dizziness, abdominal cramping, and tenesmus.

There had been no recent ingestion of raw seafood or dairy products, and no recent travel or use of an antibiotic. No other family member or personal contact had been ill. The patient, a retired farmer, lived with his wife and family.

The patient's past medical history was remarkable for a partial gastrectomy curative for peptic ulcer disease, and he also had intolerance to lactose. No previous episodes of significant diarrhea were reported.

Physical examination was notable for orthostatic hypotension, poor skin turgor, hypophonia and a dry oral mucosa. Abdominal and rectal examinations were unremarkable. The stool was green, watery and guaiac negative.

Laboratory examination revealed significant metabolic acidosis, hemoconcentration with elevated hematocrit and serum proteins and elevated blood urea nitrogen and serum creatinine. Stool Wright stain was negative. Stool culture performed on MacConkey's medium revealed non-lactose-fermenting colonies identified as *Vibrio cholera* through biochemical analysis. Serogroup confirmation was performed by the State Department of Health.

The patient's hospital course was notable for massive diarrhea production, often exceeding 1 liter per hour, marked hypovolemia, acidosis and acute renal insufficiency. Rehydration, electrolyte and bicarbonate repletion was accomplished intravenously in the intensive care unit and Doxycycline was administered. The patient was subsequently discharged in stable condition on the 6th hospital day.

Discussion

Although, in retrospect, our patient presented with many classic clinical features of cholera, the diagnosis on admission was not immediately obvious. Early differential diagnostic considerations included other infectious agents such as enterotoxigenic *E. coli*, *Campylobacter*, *Salmonella*, *Shigella* and *S. aureus*. The Zollinger-Ellison syndrome was also but less likely a consideration given the patient's previous partial gastrectomy. Other noninfectious causes of secretory diarrhea such as the vasoactive intestinal polypeptide-secreting tumors and the carcinoid syndrome were considered unlikely.

Vibrio cholera was initially considered to be unlikely. Neither the patient nor his family, all reliable historians, could reveal any history of exposure. Moreover, cholera is known to be extremely rare in Hawaii; only 2 previous cases have been documented. As a result, the quantity of stool produced was initially surprising and underestimated, which made adequate fluid resuscitation inadequate in the early hours of hospitalization.

Regardless of etiology, it is possible that the patient's previous partial gastrectomy increased his likelihood for contracting cholera, as patients with that condition or other causes of hypochlorhydria have increased susceptibility to infection¹.

Classification

There are more than 70 serogroups of *Vibrio cholera* classified based on the characteristics of the Somatic O antigen. Only serogroup O-1 is responsible for epidemic cholera; this is further subdivided into 2 biotypes: Classical and El Tor. The El Tor biotype differs from the Classical biotype both biochemically (hemolysin-producing, polymixin B-resistant) and epidemiologically (higher infectivity, causing milder infections, hardier in the external environment)². Each biotype is further subdivided into serotypes based on the presence of additional antigenic determinants.

Epidemiology

Vibrio cholera is endemic to the Ganges delta; however, 7 pandemics have occurred since 1817³. The current pandemic of the El Tor biotype began in 1961 and encompasses southeast Asia,

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Humans are the only host of *V. cholera*. Transmission occurs through human fecal contamination of water and occasionally of food (raw vegetables and seafood). However, *V. cholera* can survive in the external environment for limited periods of time.

Acutely ill patients may excrete up to 60 liters of stool over the course of their illness with 10^7 organisms per milliliter present in the stool². Direct contamination of the environment by improper handling of sewage is the major route of epidemic dissemination. Additionally, it is speculated that mildly symptomatic and asymptomatic patients play an important role in epidemics⁵.

In endemic areas, children are affected more frequently than are adults; however, it is less common in infants under 2 years of age because of passive immunity⁶. In non-endemic areas, children and adults are affected equally.

Pathogenesis

Ingestion of approximately 10^4 organisms is required to produce clinical infection⁷. The ability of *V. cholera* to colonize the lining epithelium of the small intestine is determined by adhesion factors, chemotaxis, and motility⁸. The cholera enterotoxin, responsible for clinical symptomatology, is composed of 5 binding subunits and a single activating subunit⁵. Interaction with nicotinamide adenine dinucleotide (NAD) results in increased intracellular 3',5' adenosine monophosphate (cAMP) and subsequent inhibition of the sodium-chloride transport mechanisms. As a result, active chloride secretion occurs throughout the intestine. The accumulation of isotonic fluid in the small intestine exceeds the absorptive capacity of the large intestine, producing the characteristic isotonic, bicarbonate-rich stool⁹.

Clinical Manifestations

The incubation period may vary from a few hours to as long as 5 days, but is typically 48 to 72 hours². Most cases are mild and clinically indistinguishable from other causes of gastroenteritis⁴. Severe cases are associated with the production of massive quantities of watery diarrhea often exceeding one liter per hour.

The degree of dehydration determines the severity of clinical symptoms. Severe sequelae include cardiac arrhythmias, acute renal failure, and cardiovascular collapse.

Physical findings reflect loss of intravascular fluid and include orthostasis, poor skin turgor, hypotension, tachycardia and Kussmaul respirations.

Laboratory abnormalities include hemoconcentration, hyponatremia, hypokalemia, metabolic acidosis, elevated blood urea nitrogen, creatinine and plasma protein concentration.

Diagnosis

The diagnosis of cholera is suspected with the acute onset of profuse, watery diarrhea associated with marked dehydration. The simplest technique of the direct stool examination with dark-field microscopy reveals *Vibrios* with characteristic helical motility patterns.

Immobilization by adding Group 0-1 antisera is confirmatory, if available⁶. Leukocytes are not seen on methylene blue stain. Stool culture is best performed on selective media such as MacConkey's, Monsur's, or TCBS (thiosulfate-citrate-bile salt-

sucrose) agar. Following incubation, suspected *Vibrio* colonies are confirmed by adding Group 0-1 type specific antisera. Differentiation between El Tor and Classical biotypes requires further tests for phage-susceptibility, hemolysin-production, and Polymyxin B-sensitivity.

Acute infection leads to a rise in vibriocidal and antitoxin antibody titers. Titers are elevated by the 5th day of infection, peak near the 10th day, and decline over a 6-month period². A marked rise in antibody titer in acute and convalescent serum is highly indicative of cholera⁶.

In non-epidemic settings, the differential diagnosis of choleraic diarrhea includes other pathogens such as enterotoxigenic *E. coli*, rotavirus and non-01 *V. cholera*. Rarely, vasoactive, intestinal, polypeptide-secreting tumors (VIPomas) produce choleraic diarrhea.

Treatment and Prognosis

Prompt replacement of intravascular volume and electrolytes is the primary goal of therapy. In severely hypovolemic patients, intravenous rehydration is necessary.

Electrolyte replacement, including potassium and bicarbonate, should parallel stool electrolyte losses. Oral tetracycline therapy should be instituted following rehydration to shorten disease course. Prophylaxis, however, is not recommended.

Promptly treated, cholera has a mortality rate of less than 1%⁵. Mortality of untreated cases, however, may approach 50% which emphasizes the significance of early recognition and treatment.

Conclusion

Although rare in Hawaii, cholera should be considered as a diagnostic possibility in the setting of acute, profuse secretory diarrhea, regardless of risk factors. At the time of this writing, the source of this isolated case of cholera remains obscure, and only one additional, unrelated case has been reported.

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Do we need second generation lithotripters in Hawaii?

Nancy B Crocco MPH*

Richard V Stenson MHA MBA FACHE FACMGA**

The Kidney Stone Center of the Pacific (KSCoP) currently provides statewide services for kidney lithotripsy. The non-invasive technique uses shock waves to disintegrate kidney stones. Extracorporeal shock wave lithotripsy (ESWL) can be used successfully in 85% to 90% of kidney stone patients when surgery is indicated¹.

The success of lithotripsy for the treatment of kidney stones aroused the interest of physicians treating biliary (gallbladder) disease as well as the vendors of lithotripsy devices; kidney stones affect only one-tenth as many people as do gallstones. Because of the anatomical problems in treating gallstones, design modifications had to be made to the first kidney lithotripters in order to adapt to the imaging, patient positioning, and specifically for therapy focusing required for treatment of gallstones. The Food and Drug Administration (FDA) approved clinical trials for biliary lithotripsy in the United States in 1988. It has been estimated that 15% to 30% of gallstone patients would be candidates for biliary lithotripsy².

The Kidney Stone Center of the Pacific initiated lithotripsy services for kidney stones in Hawaii in 1986 and is, therefore, the source of lithotripsy technological knowledge in the state. The KSCoP assumed the responsibility of assessing the status of the clinical efficacy of biliary lithotripsy and, if satisfied, planned to apply for a Certificate of Need (CON) to introduce biliary lithotripsy in Hawaii. A letter of intent was filed with the State Health Planning and Development Agency.

Methods

The KSCoP invited a group of physicians (gastroenterologists, general surgeons, radiologists, urologists), hospital administrators, technicians and consultants to organize themselves into a group to consult with the major vendors of biliary lithotripters and advise how to proceed with a CON application. The group met with 4 vendors during the period February to May 1990: Dornier, Siemens, Technomed and Medstone. Both a sales representative and a physician currently using the respective machines were present at each vendor meeting. Presentations included information pertaining to: Patient selection, procedure technique, technology used, localization method, results of clinical trials, comparison to other machines and acquisition and maintenance costs.

All of the lithotripters reviewed were second-generation, dual-purpose (kidney and biliary) devices. Whereas first generation devices required the patient to be partially immersed in a large water bath under general anesthesia, second generation devices are "dry", and the patient can be under either general anesthesia or intravenous sedation, but conscious. The "dry" devices included a patient-positioning treatment table and some type of fluid-filled coupling system, such as a fluid-filled bellows or a mini-water

bath built into the treatment table, or a fluid-filled bag.

The Siemens Lithostar Plus, Technomed Sonolith 3000 and Medstone STS are already FDA-approved for kidney lithotripsy. The Dornier MPL 9000 does not yet have approval for kidney lithotripsy (no device has yet received FDA market approval for biliary lithotripsy).

The KSCoP's existing unit is a Dornier HM3, a first generation device. The group conducting the analysis also considered whether a second generation device should be acquired to replace the HM3, or be used as a back-up for kidney lithotripsy until FDA approval is obtained for biliary lithotripsy.

Subsequent to KSCoP's meetings with the vendors, the FDA announced a revised protocol for a Phase II of clinical testing for biliary lithotripsy. Under Phase II, the clinical test results must be presented and compared between lithotripsy alone, lithotripsy together with bile acid therapy, and bile acid therapy alone.

Results

A summary of the distinguishing characteristics of each vendor's lithotripter follows.

Dornier

The Dornier Multipurpose Lithotripter (MPL) 9000 was operated at 10 clinical test sites for biliary lithotripsy under FDA Phase I protocol. Clinical data was presented to the FDA in October 1989 to seek pre-market approval. The FDA denied approval and requested follow-up of patients for 12 months. Dornier plans to continue clinical test trials under FDA Phase II protocol, but at a reduced number of test sites.

The MPL 9000 uses a spark-gap power source and ultrasound for localization and visualization. The purchase price is \$1.35 million. An x-ray attachment also is available for an additional \$150,000 to \$200,000. The annual maintenance fee is \$105,000; the manufacturer recommends spark-plug replacement after each procedure. The cost per spark plug is \$165; 2 are used per procedure.

A trade-in credit is available for the HM3 (the unit currently in use at the Kidney Stone Center), ranging from \$250,000 to \$400,000 depending on the age of the equipment.

The MPL 9000 does not yet have FDA approval for kidney lithotripsy, but the vendor is projecting market approval in 1991. The physician using the device reported that once the procedure has been mastered, average treatment time is approximately 30 minutes for kidney stones and 90 minutes for gallstones. The shock wave treatment technique involves first fragmenting the stone, then pulverizing it. He performed the procedures without general anesthesia and reported there were no complications. No adjustments are necessary to switch from a kidney to a biliary procedure except that the anesthesia machine had to be moved

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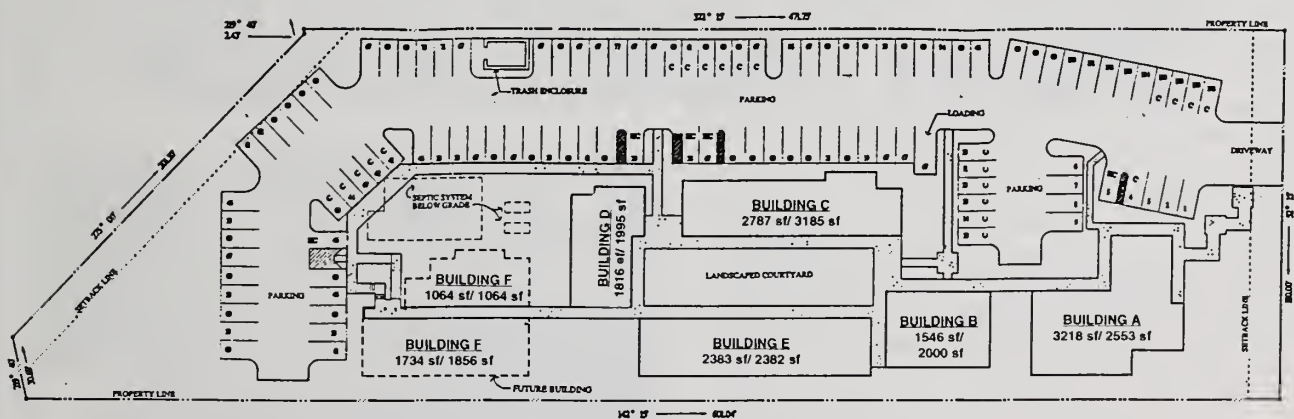
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from one end of the table to the other.

The MPL 9000 is a fixed device; a mobile model is not available. Anatomical positioning is done through the use of a 5-axis table. The therapeutic C-arm can be positioned above or below the treatment table. The therapeutic unit consists of an impulse generator, an electrode, an ellipsoid and a water cushion connected to a closed system of circulating water.

Siemens

The Siemens Lithostar Plus is available in both fixed and mobile models. There are 10 fixed clinical test sites and one mobile clinical test site for biliary lithotripsy. The Lithostar Plus is already FDA approved for kidney lithotripsy. Siemens plans to continue conducting clinical test trials under FDA Phase II protocol.

The Lithostar Plus uses an electromagnetic power source and has integrated ultrasound and x-ray localization. The electromagnetic source produces lower energy shocks than spark-gap power sources and pulverizes rather than fragments the kidney stones. For use on gallstones, a biliary attachment shock head capable of doubling the energy is attached. The gallstone is cracked at a higher energy level, then the power is lowered to pulverize the stone. Acquisition price is \$1.4 million for the fixed model and \$1.8 million for the self-contained mobile model. The biliary attachment is an additional \$300,000, annual maintenance fee is \$96,000 for kidney, and an additional \$24,000 for biliary. The shock heads are recommended to be replaced every 1 million shocks (approximately 200 procedures). Replacement cost is \$7,400 for the shock head. A trade-in credit for the HM3 is available for \$400,000.

The Lithostar Plus is designed as a urologic work station. Its therapeutic unit is ceiling mounted to allow access from all sides of the treatment table. Standard urologic accessories can be mounted on the table. A radiographic bucky cassette is built into the table to permit x-rays for checking on stone fragmentation without moving the patient. The table is computer controlled on 3 axes for positioning. The shock wave tube is water-filled and coupling bellows are placed against the patient's skin.

Because of the lower energy used, the procedure is almost pain-free and the physician reported usually using no anesthesia and performing most procedures on an outpatient basis. The physician using the device noted that clinical tests in Europe were having better results than in the United States. The reason given was that the U.S. sites were not using the low energy technique properly; treatment time averaged about 1 hour per case.

Biliary clinical test trials on 101 patients averaged 2.3 treatments per patient to obtain fragments of less than 4 mm. More clinical test data is needed before the request for FDA biliary approval is filed.

Technomed

The Technomed Sonolith 3000 is available in fixed and trans/mobile models. There were 9 fixed and 3 trans/mobile clinical test sites for FDA Phase I protocol for biliary lithotripsy. The Sonolith 3000 is already FDA approved for kidney lithotripsy. Technomed plans to continue clinical test trials under FDA Phase II protocol; however, the number of sites has not yet been determined.

The Sonolith 3000 uses a spark-gap power source with continuous-feed electrodes that may be used on 100 patients before replacement. Replacement is included in the annual main-

tenance fee. Ultrasound is used for stone localization. Acquisition price is \$1.09 million for the fixed and \$1.235 million for the trans/mobile plus an additional \$70,000 for the transport van. Annual maintenance fee is \$110,000 for the fixed and \$130,000 for the trans/mobile. The maintenance fee is reduced by \$20,000 if ultrasound is excluded from the Technomed maintenance and arranged for separately. Portable x-ray also is available for \$50,000.

The shock wave generator of the Sonolith 3000 is mounted at the base of the water basin/"minipool" coupling. The frame of the mobile sub-assembly supports the water basin. The water processing system is contained within the treatment module. Method of anesthesia is by intravenous sedation of the conscious patient or none at all.

Medstone

The Medstone Shockwave Therapy System (STS) is available in fixed and mobile models. There were 10 fixed clinical test sites and 2 mobile clinical test sites for FDA Phase I protocol for biliary lithotripsy. The STS is already FDA approved for kidney lithotripsy.

Medstone presented clinical data to the FDA in October 1989 to seek pre-market approval for biliary lithotripsy. The FDA denied approval and requested longer and more consistent follow-up on more patients. Medstone's use of historical controls did not adequately clarify the device's efficacy for gallbladder applications. Stone-free rates at six months, one of the outcomes reported varied at different test sites from 0% at 3 sites to 66% at one site. Medstone has temporarily discontinued biliary test trials and as of December 1990 did not plan to pursue the FDA Phase II protocol testing. The device is still marketed, however, for kidney lithotripsy.

The STS uses a spark-gap power source and integrated ultrasound and x-ray for localization and visualization. The acquisition price is \$1.375 million for either the fixed or mobile device. The trailer for the self-contained mobile unit costs an additional \$300,000, the annual maintenance fee is \$125,000 and the device uses one spark plug which is replaced after each procedure. The cost of a spark plug is \$270. Medstone also has an alternative pricing structure which includes a sliding-scale, fee-for-service cost based on patient volumes ranging from \$2,000 a patient to \$750 a patient. There is no maintenance fee or spark-plug replacement cost on the fee-for-service pricing.

The STS shock-wave generator is located beneath a customized x-ray treatment table. The shock-wave is focused by a curved reflector as it travels through water-based fluids contained in the reflector. A fluid-filled disposable bag couples the patient to the shock-wave generator and a computer assists in positioning the patient. The table is adjustable in 3 dimensions. The STS also can be used for general x-ray, ultrasound, and urological procedures. Lithotripsy procedures on the STS average 45 to 90 minutes in duration.

Table 1 compares the key features of each lithotripter analyzed.

Discussion

The use of drugs and biologicals

Although cholecystectomy today is considered the safest, most effective and most recommended treatment for gallstones, the pharmaceutical and biological approaches also are under study. Two types of dissolving agents being investigated with some success include: (a) Orally administered bile acid compound

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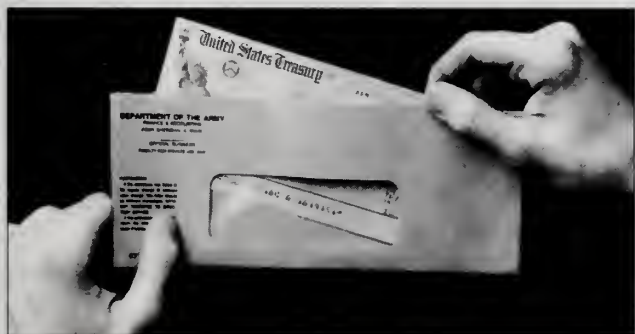
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(ursodeoxycholic acid). The medication is administered over a 1- to 2-year treatment period. A dissolving effect has been achieved only in stones composed mainly of cholesterol and no calcium salts, pigments or mucus. A research study reported a 10% recurrence rate within 1 year after discontinuation of bile acid medication³; (b) Catheter-administered cholesterol-solvent methyl tert-butyl ether (MTBE) dissolves the stones more rapidly than do bile acid compounds. MTBE dissolves cholesterol stones in an average of 12.5 hours; advanced equipment may reduce the time to less than 4 hours. The treatment must be administered carefully through a percutaneous catheter⁴.

A new surgical option

A new surgical procedure, laparoscopic cholecystectomy, has been introduced and now is being performed in Hawaii. The procedure involves the physician making only a few small (approximately half-inch) incisions in the patient's abdomen. An optical scope (laparoscope) is inserted through one incision into the abdominal cavity. The physician, viewing the operation on a video screen, removes the gallbladder through one of the small incisions. Electrocautery units and lasers are used to detach and

remove the gallbladder. The advantages of the procedure include⁵⁻⁶:

- Only 2 to 3 days recuperation, compared to 3 to 4 weeks for conventional cholecystectomy surgery.
- Reduced hospital stay, thereby reducing costs to the patient.
- Reduced scarring due to the small incision.
- Greater comfort.

Conclusions

Following the analysis, the group reached the following conclusions: Lithotripter technology is still evolving; biliary applications of lithotripsy are still investigational; the clinical efficacy of biliary lithotripsy has yet to be proven; no vendor is likely to receive FDA approval to market biliary lithotripters in the United States much before 1993; only about 15% to 30% of gallstone patients would be candidates for biliary lithotripsy due to its limited indication under the current FDA protocol for investigational use for stones of only a certain size, composition and location; and the advent of laparoscopic cholecystectomy presents a cost effective, lower morbidity, surgical option to traditional cholecystectomy surgery for patients suffering from gallbladder disease.

Key Features For Lithotripter Comparison As Of December 1990

	Acquisition List Price	Trade in Credit	Annual Maintenance	Technology	Locali- zation	FDA Approval		FDA Phase II Biliary Test Trials
						Kidney	Biliary	
Dornier Fixed MPL 9000	\$1.35 million	\$250,00- 400,00	\$105,000	Spark Gap Single Use Electrode	Ultrasound X-ray Attach- ment Avail (\$150,000- 200,000)	No- Project 1991	No	Yes
Siemens Fixed Lithostar Plus	\$1.4 million +\$300,000 Biliary Attachment	\$400,000	Kidney- \$96,000+ Biliary \$24,000	Electromagnetic	Ultrasound & X-ray Integrated	Yes	No	Yes
Siemens Self Contained Mobile Lithostar Plus	\$1.8 million +\$300,000 Biliary Attachment	\$400,000	Kidney- \$96,000+Biliary \$24,000	Electromagnetic	Ultrasound & X-ray Integrated	Yes	No	Yes
Technomed Trans/ Mobile Sonolith 3000	\$1.235 million +Van (\$70,000)	Willing to Discuss	\$130,000 (-\$20,000 if Ultrasound excluded) (Includes replacement Electrodes if needed)	Spark Gap Continuous Feed Electrode	Ultrasound Portable X-ray X-ray Avail	Yes	No	Yes
Technomed Fixed Sonolight 3000	\$1.09 million	Willing to Discuss	\$110,000 (-\$20,000 if ultrasound excluded) (Includes replacement electrodes if needed)	Spark Gap continuous feed electrode	Ultrasound Portable X-ray avail (\$50,000)	Yes	No	Yes
Medstone Fixed STS	\$1.375 million or Fee-for- Service (\$2,000 to \$750/patient)	Yes- Negotiate Amount	\$125,000 (\$0 on Fee- for Service)	Spark Gap- Single Use Electrode	Ultrasound & X-ray Integrate	Yes	No	T/D*
Medstone Self Contained Mobile STS	\$1.375 million + Trailer (\$3000,000)	Yes- Negotiate Amount	\$125,000	Spark Gap- Single Use Electrode	Ultrasound & X-ray Integrated	Yes	No	T/D*

*Temporarily Discontinued

The overall conclusion of the analysis is that biliary lithotripsy should not be introduced in Hawaii until the clinical efficacy and cost benefit of the service can be demonstrated.

The KSCoP will continue to monitor the technologic progress of biliary lithotripsy and alternative treatments of gallstones. At such time that a responsible decision can be reached that Hawaii would benefit from the availability of biliary lithotripsy, the KSPoP will submit a CON application to establish the service in Hawaii.

The group further concluded that a second generation device should not be acquired at this time as either a replacement for the current Dormier HM3 or as a back-up. Major reasons include: The cost of health care would be unnecessarily increased without any improvement in the quality of care; additional capacity is still available from the existing HM3; the State does not have a need for a second kidney lithotripter as yet; physicians using the existing HM3 are satisfied with its performance and the device has rarely needed down time due to mechanical problems; physicians in the group conducting the analysis preferred the use of general anesthesia because of the controlled respiration which reduces the time required to perform the procedure as well as the number of shock waves required; and physicians noted that re-treatment appeared to be necessary more often when the second generation devices were used (21%)⁷, were used as compared with the current experience with the HM3 in Hawaii (9%)⁸.

ACKNOWLEDGMENTS

The group conducting the analysis for the Kidney Stone Center of the Pacific

included: James Grobe MD, Howard Minami MD, Stanley Shimoda MD, William Morioka MD, Gene Robinson MD, Bradley Wong MD, Howard Arimoto MD, John Cieply MD, Curtis Kamida MD, Thomas Ito MD, James Stewart MD, Walter Strode MD, Kuakini Medical Center Gary Kajiwar, Queen's Medical Center Constance Wiletzky, Straub Clinic & Hospital Richard Stenson and Hospital KSC Administrative Manager Stephen Knoll; Supervisor, Doris Oshiro, Special Procedures Technologist, Marlaine Fern, Marketing, Ellen Kumata, KSC Marketing, Garrett Kawamura and Nancy Crocco Ernst & Young.

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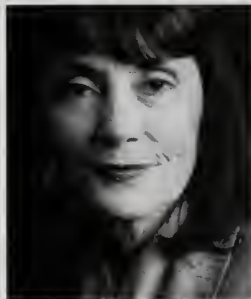
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Henry N Yokoyama MD

Hawaiian Rent All Signs:

(Corner of Beretania and McCully)

"We hope you celebrate Thanksgiving...with a fowl mood."

"If you don't vote Tuesday...don't complain Wednesday."

"Our dollies can't talk...but they sure can move."

Marjie's Sign

Marjie, our spouse, is mother of 6, gardener *par excellence*, superb cook, companion for our golden retriever, Duke, and normally an even-tempered, gentle, God-fearing citizen. We come home one evening and there on our front lawn is a large hand-scrawled sign: "Warning! Pick Up Your Dog's Mess!" (without even that neat word 'Please') Something is amiss. We sense a crisis, inquire within, and learn that she has been picking up dog droppings every morning for more than a week. She feels strongly that it is time the dog-walker pick up his own dog droppings as she does Duke's on their walks. She knows from the size and texture that it is the same large animal; she is furious because she has been unable to catch and confront the dastardly felon. The very next day the deposits shifted to our neighbor's lawn. Several days later, Marjie announced exuberantly that none other than Leon Edel of Henry James-biography fame had paused his daily walk to comment: "It's short and direct...and you say it has worked? That's even better."

Life In These Parts

Honolulu may become one of 50 study sites for a massive multi-million dollar Women's Health Initiative by the National Institute of Health that will look at estrogen and other things. Epidemiologist/internist/geriatrician David Curb of the Honolulu Heart Program at Kuakini will be chief investigator. Already, \$500 million has been allocated to cover the impact of hormones on heart disease, breast disease, endometrial cancer, colo-rectal cancer, osteoporosis, and the psycho-social impact of menopause.

Medical Fact or Fantasy?

Internist Myron Shirasu has seen interesting medical statistics showing baby girls result from lovemaking in the backseat of a car. The relative decrease in female births in recent years is attributed to the decline of drive-in theaters, according to Myron.

Kozo Sushi of Hawaii

The sign at the counter said "Our Sushi Is Guaranteed Two Hours After Purchase." We had visions of the delicacies disappearing in puffs of smoke after 2 hours.

Medicaid Dilemma (Excerpts from a Jan 13 *Honolulu Star-Bulletin* editorial)

The medicaid program in Hawaii is moving closer to the \$400-million mark. Last year the State had to come up with \$64 million to meet a Medicaid overrun, and the overrun is expected to approach

\$80 million this year. Medicaid eligibility (presently 84,000 patients) is expected to reach 98,000.

Nationally, Medicaid is part of a health-care industry expected to cost more than \$900 billion or 1/7 of the entire economy.

The reporter predicts: "Ultimately, limits must be part of the solution. Those suggesting managed care as an alternative to Medicaid have good intentions but need market evidence to show it can work. Hawaii has great health-care ambitions, including the Family Hope long-term care proposal and a proposed commission to monitor health costs. People must be cared for, but in trying to provide that care for all, Hawaii has created a system that already seems more expensive than we can afford."

Family Hope

(Developed by the state's Executive Office on Aging by directive of the 1991 Legislature).

Means a new tax of 0.6% of adjusted gross income.

Benefits:

Year 1= No benefits.

Year 2= Adult day care and respite care eligibility for 600,000 *bona fide* Hawaii residents regardless of income.

Year 3= Home and in-community care added.

Year 4= Nursing-home care added.

Why? Alternatives will be worse.

In the 1980s, the population of people 65 and older increased 87% while the overall state population increased only 14%.

Nursing-home care costs \$45,000 a year today and may rise to \$200,000 by year 2020.

How will it work?

The tax levy will be paid into a pool like the federal social security reserve. The fund will be increased by funds diverted from Medicaid.

Services will be provided by private enterprise, but funded by the pool with a 20% copayment by beneficiaries.

A small administrative board of 3 full-time professionals.

Proof of Family Hope tax payments required (to preclude nonresidents).

The full phase-in of benefits will require 4 years with no benefits the first year.

People too poor to pay the qualifying tax will remain on Medicaid.

- If adopted, Hawaii will be the first in the nation.

- At the start, an estimated pool of 600,000 taxpayers will pay an average of \$160 a year each and no more than \$1,050 because of an income cap with no tax on income over \$250,000 and a reduced tax over \$100,000.

(The above information was gleaned from A.A. "Bud" Smyser's "Hawaii's World" in the *Honolulu Star-Bulletin* 12/15/92.)

Out In a Limerick by Heywood Broun

There was a young man with a hernia
Who said to his doctor, "Gol dernia,
When improving my middle,
Be sure you don't fiddle
With matters that do not concernia."
(From *Reader's Digest* Oct '92)

A patient called his doctor about a lump in his groin. Doctor: "Put on a hot compress and the lump should go away." The doctor saw the patient at the supermarket a week later. "How's the lump?" "Oh, the lump is gone. I started to put on a hot compress, but my cleaning lady told me to use a cold compress and the lump was gone next day." Doctor: "That's funny! My cleaning lady had said to use the hot compress."

(As told by Jim Stewart during his Queen's Friday morning lecture January 8. "U.R. It!" to illustrate a point about options.)

Hors de Combat

After deliberating 5 hours, a Big Island jury cleared surgeon Lawrence Peebles of malpractice and silicone-breast manufacturer, McGhan Medical Corp. of negligence. The patient had breast implants in Florida 12 years earlier and in 1984 Larry had replaced her Rt breast implant which had hardened. (There is still some justice in this world.)

Physician Moves

December: Straub's Newest Physicians are:
Dermatologist Jenifer Fong - Pali Momi
Internist Michael Kurosawa - Pali Momi
Endocrinologist Frank Singer - King St
Internist Katherine Williams - King St

Internist Kimiko Naiki relocated to Queen's POB II Ste 107.

January:

Dennis Crowley, board-certified in pediatrics, physical medicine and rehabilitation, and electrodiagnostic medicine opened his practice at Queen's POB Ste 804.

Pediatrician Jeffrey Lim assumed the practice of Marcia Nagao at 2525 S King St Ste 308.

Orthoped James Miller, Jr relocated his orthopedic surgery and sports medicine practice to Aiea Medical Bldg, Ste 505 and to Pan Am Building, Ste. 1333.

General surgeon Albert K.S. Chun, known to his friends as "Bozo," retired from active medical practice effective Feb. 1.

Miscellany—Friendly banter from Beretania Tennis Courts

"Did you hear about the dentist who married a manicurist? They got divorced after a month because they fought tooth and nail." (As told by Clay Benham.)

Three boys were bragging about how fast their dads were. The first kid said, "My dad is the fastest. He is into archery, he goes to the range, shoots an arrow and beats the arrow to the target." The second kid said, "That's nothing. My dad is faster than yours. He goes to the rifle range, aims, fires his rifle and overtakes the bullet." The last kid said, "My dad works for the City and County. He is so fast that he punches out at 4pm and is home by 2!" (Another Clay Benham contribution.)

Hors de Combat Medicare Fraud

The largest Medicare fraud case in U.S. history was settled with the National Health Laboratories of La Jolla, California, which was assessed \$111 million for fraudulent charges to Medicare, Medicaid and health care programs for military families.

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubiaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral alpha-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

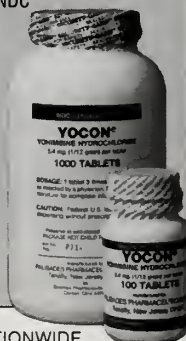
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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STRONGYLOIDES INFECTION IN HAWAII

(Continued from page 61)

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"I've told you time and again, Harriet,
I do NOT want a cuckoo clock for my office."

Maka O Ke Kauka

Russell T Stodd MD

Sooner or later the worst possible set of circumstances is bound to occur.

A 91-year-old man drove down a hill, suddenly veered across the center line, crashed into an oncoming car, and then ricocheted off several others. Five people, including the elderly driver, died in the collision. Multiple lawsuits resulted, including complaints against 2 doctors. The allegation was that the doctors were guilty of general negligence for not informing the patient's family of his condition so the relatives could have taken action to prevent his driving. The case was settled out of court for a "sizeable sum." The lesson here is apparent: If the physician believes, for whatever reason, that the patient should not operate a motor vehicle, then it is vital to so state to the patient, to a responsible member of the family, and to make such notation in the record.

"Never send to know for whom the bells tolls..."

After years of discussion, confrontations and legal gyrations, HCFA has finally given birth to Gail Wilensky's dream and settled on the ophthalmologists and other providers for cataract surgery reimbursement through a bundled price. And the winners (?) are: (1) Cataract Eye Center of Cleveland; Fairview Regional Eye Institute, Cleveland; Medical Eye Associates of Middleburg Heights; and (2) Surgical Care Affiliates/Ft. Worth Surgery Center; Doctors Hospital of Dallas, et al; and (3) Southwestern Eye Center, Mesa Ltd., Phoenix. The negotiated cataract package prices range from \$2,194 to \$2,513 (plus inflation and other adjustments). Medicare expects to save from 5% to 20% on an estimated 15,000 eye procedures during a 3-year period.

Where was Kusserow when he might have been useful.

National Health Labs of LaJolla, California, pleaded guilty to Medicare fraud and agreed to pay more than \$110 million reimbursement. By over billing and government for certain lab tests, the company claimed it was merely following "common industry practice," but Medicare claimed it was fraud. Now the company's CEO also pleaded guilty, resigned his post, and faces a possible fine of \$500,000 and up to 10 years in prison.

Crime does pay—at least for somebody

The above crime was prosecuted by a former manager of a competing firm. He brought suit on behalf of the government under the False Claims Act. The law provides that plaintiffs receive 15% to 25% of payments to the government; therefore, the whistle-blower stands to come into a sizeable reward—like \$15 million+? Holy stool pigeons!

This makes for dull reading, but you must pay attention!

The Health Care Financing Administration reimburses hospitals on a DRG-based PPS (Prospective Payment System). While the initial payment rate in 1983 was designed to be budget neutral, Medicare payment for the first 2 years far exceeded hospital costs. Result: hospitals prospered.

However, since then, the annual increase of Medicare payments has been lower than increases in hospital costs per admission. Result: the lines crossed in

1988 and are rapidly diverging. Total Medicare inpatient payments now have gone substantially below costs. Result: to remain solvent, hospitals are forced to charge private patients considerably in excess of their costs. On average, private patients now pay 128% of costs! These payments by private patients generated a net surplus of \$22.5 billion!

The outcome here in the land of aloha is that HMSA and Kaiser have continued to raise their premiums, as they must to stay out of the red. So let us all recognize that every dollar paid for health insurance partially provides for Medicare/Medicaid underpayment, a hidden but very real indiscriminate *tax*. How long will this abuse go on? Somewhere down the road hospitals, insurers and private payers will be forced to tell Congress and Medicare, "enough, already"! And that is but one reason why the AMA has continued to fight physician DRGs.

(Continued) ➤

◆ How to Invest in Biotechnology ◆

How do you invest successfully in biotech anyway? It's a good question.

THE GRIM TRUTH

The answer is simple if not easy. It can be summed up in one word—**homework**. Yes, that's the grim truth. To invest successfully in biotechnology you have to **do your homework**—and plenty of it.

Here's how we think you should do your homework if you really want to make money investing in biotechnology.

HOW TO INVEST IN BIOTECH

At **Biovest**, where we **specialize** in biotechnology money management, we believe strongly that successful biotechnology investment is driven by investing in sound science.

The bald and basic truth is that to rationally invest in an industry as scientifically complex as biotechnology you need to do some real work! You can't just throw darts at a board or "read a chart" as much as people would like it to be that way.

We think what you really need to concentrate on if you're investing in this area is whether or not the phase 1, 2 and 3 trial data are showing statistically significant safety and efficacy data.

What do you think?

HOW TO DO IT RIGHT

Here's what we think **you** should be doing, or **someone should be doing for you** if you want to invest correctly in Biotechnology.

First we think you need to do **sound and**

thorough scientific analysis, and at Biovest, we pull and read research papers routinely.

You also need to **attend scientific conferences**, and at Biovest we do this regularly too (for example ICAAC, ASCO, ASH and others).

You need to **visit the companies** and engage the management and scientists in ongoing dialogue, and at Biovest we do this with virtually **every company** we invest in.

You also **need a thorough understanding** of the process of new drug approval (INDs, phase 1, 2, 3 trials and FDA requirements). At Biovest we attend advisory panel meetings and actually talk with members of FDA advisory panels and boards when we can.

You need to **have a sound financial model for stock pricing**, and a sound portfolio management theory and at Biovest we have a proprietary financial model that has proved very successful over the years.

If all this sounds like a **lot of work**—you're right. It is.

PUT THE ODDS ON YOUR SIDE

If you think **you can't do all this for yourself**, you can put the odds for successful biotechnology investment strongly in your favor by **giving us a call at Biovest**. We are SEC registered money managers domiciled in Hawaii. We stress a long term, scientifically oriented approach to biotechnology investment.

For an investment consultation or for a free copy of our newsletter, **please call us at 808-988-5345**, 24 hours a day, 7 days a week.

Rostenkowski—Man of the People!

Illinois Representative Dan Rostenkowski is Chair of the House Ways and Means Committee, a very powerful position with control over the government's purse strings. He allegedly spent \$99,000 of his political contributions to rent office space in a family-owned building and to purchase stamps from the House post office. Isn't it comforting to know he is watching over your tax dollars? What a guy!

Addenda

- ▲ In a series of 33 patients with central serous chorioretinopathy, 90% had undergone very distressing experiences before the first attack.
- ▲ Ratio of federal dollars spent in 1991 on S&L and bank bailouts to federal dollars spent on welfare was 6:1.
- ▲ If something is confidential, it will be left in the copy machine.
- ▲ After the party, give your partner *effleurage*. She or he will be ever so grateful.
- ▲ At the inauguration of our President did the Marine band play "Inhale to the Chief?"

Aloha, and keep the faith

rts
■

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NONMEMBERS, please call Leilani at 521-0021. Four-line minimum, approximately five words per line. Rates are \$6.40 per line.

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Medical Clinic For Sale. Internal medicine primary care practice. Located at the Aiea Medical Bldg. Fully equipped & fully furn. Estab. 15 yrs. 25 patients/day, 3 exam rms., consultation rm., business/billing office, recep. area, complete in-office lab. Office approx. 950sf. Terms negotiable. Serious inquiries & offers call: 528-2102; 622-7611 or write Medical Clinic, PO Box 2167, Hon., HI 96805.

EMPLOYMENT OPPORTUNITY

Aloha Medical Consultants — Positions available 6MDs: Internists/Ob/Ortho/Occ. Health+; Charge RNs and RPTs. Kathryn Beavin 941-1551.

FP/GP. For Maui resort medical office. Send CV to Dr. Ben Azman, West Maui Healthcare Center, Kaanapali, Hawaii 96761 or phone 1-808-667-9721.

Internist and/or Medical Oncologist needed to join active practice. This is an excellent opportunity to develop a busy practice in a short period of time. Please call 244-7627, Wailuku, Maui.

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Electrocardiograph — Burdick Model E310. Prints 12 lead report on 8-1/2" x 11" sheet. \$900 complete. Contact Marika at 831-3000.

OFFICES

Medical Office Space — Established medical office space to share at 1040 South King Street, Suite 312, Honolulu, Hawaii, 96814. For information, please call 531-8576.

Medical Office available for rent from August 1993 (1060 sq. ft.) Kuakini Medical Plaza Bldg. Contact Dennis 538-6622.

Furnished offices available to share — Mon, Wed, Fri at St. Francis Medical Center-West. Tue and Thu at Medical Arts Building. 1010 So. King Street: call 671-0188.

Large Psychiatric Practice — willing to share office space downtown Honolulu office location and Hilo office location, complete with staff, managerial and billing support. Please contact Jon Won at HMA, 536-7702 for information.

Lower Your Overhead — Nice conf. rms. & offices available. Hourly and full time, receptionist, tele. ans. in YOUR name, much more, EXCELLENT IMAGE. Call HEAD-QUARTERS COMPANIES 522-9494.

Pan Am Building — Ground floor office suites available. Great location for a new or relocating practice, competitive rents and terms. Great prkg. Call to see what's avail. & discuss your requirements. Wagner & Wagner Inc. 944-8100

Sports Medicine and Orthopedic Surgical Practice willing to share office space at Queen's POB-1 and Pali Momi POB location, complete staff, managerial system, radiology and physical therapy services available. Contact Diane Fong at 536-4992 M-W-F or 487-7231 T & TH.

Ambulatory Surgery For Sale or Lease — Located in a medical office building. Fully equipped and furnished. Terms negotiable. Call 538-6622; or write to: Ambulatory Surgery Center, 1520 Liliha St., Suite 601, Hon., HI 96817.

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Internist retiring after 37 years of active practice. Large and busy practice. Convenient location on South King Street. Call 536-4654 to discuss terms.

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PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.** Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic 6 α -hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *in vitro* antacids (1 hour prior to PRAVACHOL), cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitals, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a \geq 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear (Wallerian-like degeneration and retinal ganglion cell chromatolysis) in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye (Harderian gland) (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/– mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg/day or in rabbits at doses of up to 50 mg/kg/day. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthena, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

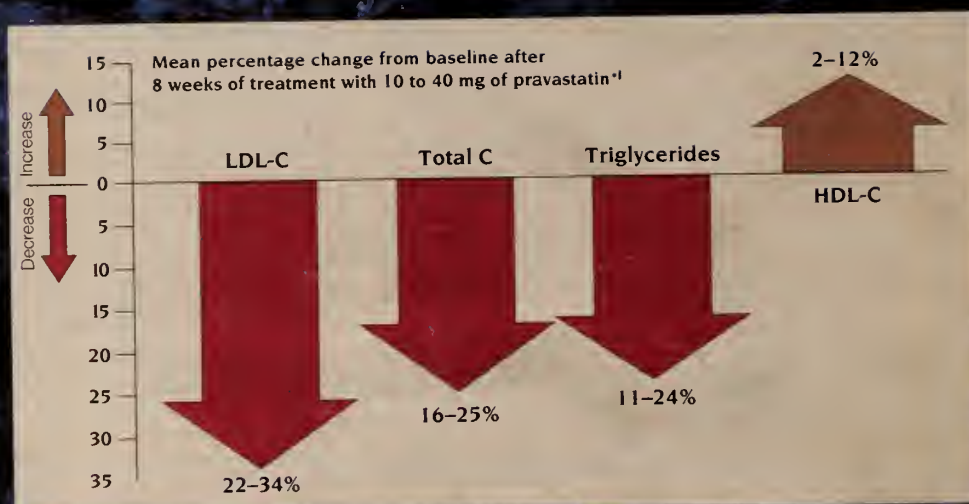
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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

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Highlights of the HMA Council Meeting of March 5, 1993

The HMA Council met on 5 March 1993. Members present were: J Chang, A Don, J Spangler, S Wallach, C Kam, R Stodd, L Howard, C Lehman, B Shitamoto, R Lee-Ching, M Cheng, R Goodale, HKW Chinn, P Chinn, HH Chun, W Dang Jr, P Hellreich, M Shirasu, C Wong, C Kadooka, P Kim, J Betwee, H Percy, T Smith, G Goto, J Lumeng, W Chang, N Winn, A Kunitomo, J McDonnell, WWL Dang; F Reppun, Editor, HMJ; Legal Counsel Vernon Woo; Auxiliary representative, Penny Paik Thune; medical student M Rivera and guest Director of the DOH J Lewin; HMA Staff: J Won, L Tong, J Asato, and A Rogness (recording secretary).

President Dr Jeanette Chang and Executive Director Jon Won joined AMA in Washington, DC, during spring break for a "New Partnership" with Congress and President Clinton; physicians are asking government to collaborate on joint efforts to address the health care access and health care reform issues.

Treasurer John Spangler reported the HMA will not experience a deficit for 1992.

The HMA Auxiliary reported on its projected May 23, 1993, Fashion Show at the Sheraton Waikiki with loads of physicians as models as well as their spouses. It pleads for physicians to buy tickets to benefit the Waianae Coast Comprehensive Health Center Scholarship Fund for health care education.

The Council adopted a 5-year dues structure pilot program for young physicians (already defined) with 20% added each year of regular membership until full dues are reached by the 5th year as an incentive for younger physicians to join and remain within organized medicine.

There was much discussion about the proposed Hawaii Health Commission by the legislature, wherein a governmental body will collect data, including specific and individualized data on providers for analysis and dissemination to the public so the public can choose health care services wisely. HMA opposes the current bill but would support data collection and public education on a joint and collaborative public/private-sector approach.

The Council approved financial support for a Forensic Science Fair to be held at the Honolulu Police Department in conjunction with the Department of Education.

It also approved mailing an educational letter to physicians statewide to apprise them of the quality-of-care issue and provide new data received regarding nurse prescriptive authority.

Legislative issues show HMA positions being upheld in a vast majority of cases, including (at time of this writing) these bills that are still alive: 1) blood alcohol level to be changed from 0.1 to 0.08; 2) Involuntary testing for HIV if the patient's blood is already drawn and if exposure to health care workers has occurred; 3) A family practice residency program at Hilo; 4) The County State Hospital to be autonomous; 5) An increased tax on cigarettes. Legislation on prescriptive authority by nurses is dead for this year.

The Council was reminded that Distinguished Medical Reporting Awards will be given at a gala banquet on April 24, 1993; all councilors should sign up for this event.

Fred Holschuh
HMA Secretary



Tamoxifen: Pro and Con

The following, submitted to the *Journal* by Steven Moser MD of Maui, was sent to us as a letter-to-the-editor. Under our mandate to have manuscripts peer-reviewed prior to publication, we received mixed responses. It was generally agreed that the subject matter warranted free and open discussion as presented to our readers.

However, since the National Cancer Institute (NCI) has already formulated the program of the National Surgical Adjuvant Breast and Bowel Project (NSABP); and since it has been endorsed for Hawaii by the Cancer Research Center of Hawaii (CRCH), we thought it best to juxtapose this article with a response

from Virginia Pressler MD of Honolulu, who is the local State Project Director for CRCH, in the same issue of the *Journal*. Moser is on the con side, Pressler on the pro side.

Consequently, instead of publishing these points of view as letters-to-the-editor, we have put both under a new heading of "Controversy".

We trust our readers will be interested and will derive benefit from these two presentations in terms of being able to communicate better with their patients as the latter challenge their physicians.

The Editor



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Long-term care (LTC)

The HMA's Senior Physicians Committee started the year by discussing LTC. At its January 7 meeting, the 20 or so members under its chair, Charlotte Florine, listened to guest speaker Calvin Ichinose, Administrator of Skilled Nursing Facilities at Queen's Medical Center (QMC). On February 4, the guest speaker was Randy Havre, Chair, LTC Financing Board, of the State's Family Hope Program.

Calvin Ichinose gave us some important figures: We have 40 facilities on Oahu, a total of 3,400 beds. The national average is 56 beds per 1,000 population; in Hawaii it is 26 beds, most of them home care. Eighty percent of these beds hold Medicaid clients. SHPDA allowed the establishment of 772 new beds in 1993, of which 712 were supposed to be built/made available in the Honouliuli area. However, the Sierra Club's \$42 million suit against the City to force it to elevate the Honouliuli sewage treatment plant to a secondary level has stymied any further expansion of housing in the area.

QMC — a 500-bed hospital — has applied for a Conditional Lease Permit to build 180 skilled nursing facility beds, but this has been denied so far. QMC has 120 beds tied up by LTC patients as an average at an annual loss in revenue of \$1.2 million.

Ichinose pointed out that the OBRA regulations under the federal law are so demanding, without a thought to the resultant costs of the program, that there is not much incentive for private entrepreneurs to build LTC facilities.

Randy Havre explained why he accepted Governor Waihee's request to serve on the Financing Advisory Board. It was with the provision that Havre would be free to express his opinion as to whether the Family Hope Program was worth the effort or not (the members are all volunteers). Havre had spent a total of 100 hours of work on it so far, together with Harlan Cadinha.

They attacked the challenge by projecting it 75 years ahead, and formatted 11 legislative guidelines rather than 3 or 4 scenarios.

As well as we could catch Havre's rapid-fire expression: (1) Every tax payer in Hawaii (some 600,000) would be taxed according to adjusted gross income—making for a broad base of contributors. (2) Benefits would be vested in a time frame: 50% at once and an added 10% each year times 5, at which full benefits

would ensue. (3) In the long-term, premium payments at 0.025% annually would cease after 40 years. (4) Incoming new residents would be included in the tax-base. (5) Community-based home health care would be promoted, starting at an ADL level of 2. (6) Participation would be on the basis of individual social security numbers, not by couples or families. (7) Maximum co-payment to discourage over-utilization would be limited to a ratio of 80/20 and the cap on such out-of-pocket contributions would not exceed an amount comparable to what one would have to pay in the way of an annual premium for private LTC insurance.

Havre made a good presentation; he also said that John Wilkens, the Program's actuary, was well qualified and was highly rated by *Consumer Reports*. He said the program would be sent out on bid to various private insurers who have the means and expertise to assess the financial aspects of the program.

In answer to the Chamber of Commerce of Hawaii's objection that the program would cost the taxpayers of Hawaii 15% to 30%, instead of 0.025% as envisioned overall, Havre explained that the savings to the State further along in the way of reduction of the costs of LTC for Medicaid clients would result in the tax being kept low (does this actually mean that the people are to pay early on and the State to be reimbursed later? Is that fair?/Ed).

Our own Walter Quisenberry followed up by citing and reading excerpts from the cover story on LTC in the magazine *Hawaii Investor*. Readers are encouraged to read a copy: the article by Lucy Jokiel is well-written.

To editorialize briefly: It is our view (not necessarily that of the HMA, which has not stated its case so far) that the matter of financing LTC falls far behind the urgent need to provide universal access to medical care, locally as well as nationally. We feel that LTC is very much a personal problem—for individuals to forsee and to fund on their own while they are still young and productive, either by savings and investment or by purchase of insurance while the premium is low. We do not feel it is a societal problem as compared with the access to medical care.

And, the 2 should not be combined in considering legislation to effect universal access.

The Editor

Lipomas

There is very little in the literature of the past 12 years that has been written on lipomata, as a recent Med-Line search has revealed.

That, together with a suggestion from a former member of the HMA Publications Committee, proposing that we establish a regular column in the *Journal* and name it "Tricks of the Trade",

wherein physician readers might volunteer to announce techniques that work, offbeat items that might save time and effort on the part of the physician and also save costs to the patient or his or her insurer, makes us think that Reinking and Parsa's brief article in this issue of the *Journal* might be of interest to our readers.

The Editor



...a matter for doctor/patient decision.

Tamoxifen: A caveat on the con side of the debate

Steven M Moser MD*

Having reviewed the recent literature on the anti-estrogen drug tamoxifen, I am concerned about the recently initiated National Cancer Institute (NCI) clinical trial to determine the worth of tamoxifen for preventing breast cancer in healthy women, the NSABP (National Surgical Adjuvant Breast and Bowel Project) Protocol P-1. This \$60-million trial will enroll 16,000 women: half placebo controls, and the other half tamoxifen subjects. The latter group includes all women over the age of 60, and women between the ages of 35 to 59 whose minimum 5-year risk is at least that of a woman >60 (calculated by a composite mathematic model weighing family history, age of menarche, number of relatives with breast cancer and other factors).

While there does not appear to be a problem with enrolling women with the highest risk of developing breast cancer in such a trial (those with the diagnosis of lobular carcinoma in situ or those who have both a mother and a sister with breast cancer), the current study design of subjecting all 60-year-olds as well as younger, lower-risk women to prolonged tamoxifen exposure may not be warranted, based on several recent studies that have been released since the protocol was completed. This may be especially true for Hawaiian and oriental populations for reasons that will be explained.

Tamoxifen was chosen for this trial because it has been shown in several large studies¹⁻⁴ to reduce the recurrence of contralateral breast cancers in women who have had estrogen receptor-positive (hormone sensitive) primary breast cancer. These studies were all short-term, actuarial trials in nature, looking only at survival rates and disease-free intervals and did not routinely include biopsy or autopsy examinations of study and control groups. This may have led to an underestimation of new, non-metastatic malignancies that were either missed or mistaken for metastatic breast cancer.

This is an important consideration because of the animal and human studies that have demonstrated tamoxifen to be a cancer promoter in uterine, hepatic and estrogen receptor-negative breast cancers. In the Swedish study³, there was an excess of nonfatal endometrial cancers in the test group (1.4% tamoxifen group vs 0.2% control group). There are several case reports of uterine cancer in women taking tamoxifen⁵⁻⁷. When

combined with the new evidence that tamoxifen is a teratogen in the developing female genital tract, with strong similarities to diethylstilbesterol⁸, these studies predict a danger to both postmenopausal and premenopausal women that is not sufficiently addressed in the current NSABP P-1 Protocol and its informed consent form (1/24/92 version).

Postmenopausal women who have not had hysterectomies are required by the protocol to have pelvic examinations at initiation of the study and every 12 months thereafter. The study protocol states that in the case of menstrual irregularities which persist in the face of normal pelvic exams, the patient should undergo further testing such as hysteroscopy or dilatation and curettage (D&C). These expensive procedures, as are all office exams, lab tests and procedures, are charged to the patient, which might prove to be a deterrent to careful follow up for uninsured or indigent patients. The possibility that endometrial carcinoma may develop in patients without obvious menstrual irregularities until late in the course of their cancer is not addressed. Untreated uterine carcinoma is a major cause of morbidity in women who have it.

Premenopausal women in the study are advised on the one hand not to become pregnant, as tamoxifen is a human teratogen, and on the other hand, they are told not to use birth control pills because estrogens will interfere with the action of tamoxifen. It is well-known that barrier methods of birth control have a high failure rate⁹, as does the rhythm method. The consent form also discourages the use of IUDs because they promote menstrual irregularities. These factors, when coupled with the clomiphene-like propensity of tamoxifen to increase fertility, may increase the likelihood that premenopausal women may indeed find themselves pregnant while taking tamoxifen. At this point, the protocol and the informed consent form also fail to provide funding or moral and legal support for the abortion which would presumably be indicated.

Tamoxifen is a known liver carcinogen in rats. At doses of 35 mg/kg/day, it caused hepatocellular carcinomas at between 31 and 37 weeks of use¹⁰. Other studies have shown carcinogenicity at lower doses. At an average of 40 kg to 60 kg weight for an average 60-year-old woman in the study, the margin of safety is somewhat less than a factor of 100, which is the accepted standard of protection for humans in the face of a known carcinogen. The half-life of tamoxifen is longer in humans than in rats, which may further compromise this safety factor. The tumors in rats are highly malignant, perhaps explained by the finding of the induction of covalent DNA adducts with tamoxifen, with mutations occurring within a few days of starting the drug¹¹.

(Continued) ►

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The Swedish tamoxifen trial³ found 2 liver carcinomas in its study population, which was several-fold higher than the average incidence of this tumor. As mentioned before, other studies have either not looked for it or may have mistaken it for metastatic breast cancer. Very few healthy women have taken tamoxifen for more than 5 years, and therefore very little adequate human data have been obtained to conclude that tamoxifen is or is not hepatotoxic in humans¹². The NSABP P-1 protocol does not call for specific liver function testing but mentions only "chemistry tests" to be done every 6 months.

In other work published this year and not referenced by the study protocol is a work by Zimmisky et al in which tamoxifen was found to promote growth of dimethylbenzanthracene-induced, hormone-independent tumors in the rat mammary gland. While growth of hormone-dependent tumors was, as expected, decreased significantly in the tamoxifen group, hormone-independent mammary tumors developed during tamoxifen administration and displayed "...extremely rapid growth"¹³. These tumors grew 3 times faster than similar hormone-independent tumors in control animals, as well as significantly faster than hormone-dependent tumors. In the discussion of this paper, the authors point out that tamoxifen has been shown in other studies merely to delay the onset of hormone-sensitive tumors.

Fentiman, of the Royal Marsden Hospital in London, points out that tumors in younger women are likely to be receptor-negative, and goes on to say, "If, however, the malignant phenotype ie receptor-positive is inhibited for say 2 to 5 years, with subsequent emergence of a more aggressive hormone-independent variant, the prognosis might be worse if no tamoxifen had been given"¹⁴.

In Hawaii, this consideration of induction of estrogen receptor-negative malignancy carries greater significance because of the greater prevalence of estrogen receptor-negative disease that our Japanese population exhibits¹⁵.

Other considerations involve the significant incidence of ocular toxicity and thrombophlebitis in women receiving tamoxifen. In a prospective study of 63 women receiving low dose (20 mg/d), long-term tamoxifen, 6.3% of the subjects developed retinopathy and/or keratopathy from between 10 to 35 months of initiation of therapy¹⁶. Unfortunately, the protocol and the informed consent do not mention the probability of ocular disease development at low doses of tamoxifen to either the investigators or to the prospective study enrollees, and does not recommend or provide for either routine ophthalmological exams or slit-lamps, both of which should be mandated based on this and other information.

In the NSABP B-14 Trial, 3 of 1,414 women in the control group and 18 of the 1,403 women in the tamoxifen group developed deep venous thromboses or embolism. Two deaths occurred from pulmonary embolus¹. If this incidence is extrapolated to 8,000 healthy women, some of whom have an increased statistical risk of developing breast cancer, we can expect approximately 80 of them to develop deep venous thrombosis or an embolic event, and around 9 or 10 of them to die of massive pulmonary embolus.

In addition, there is ample evidence that tamoxifen causes significant side effects in those who take it over the long term. In

a recent study of 140 patients receiving adjuvant tamoxifen therapy, 17% had moderate to severe vasomotor symptoms and gynecologic symptoms in 4%¹⁷. In their conclusions, the authors state, "...this study suggests that in a population of postmenopausal women with a history of axillary node negative breast cancer, almost half of the tamoxifen-treated women will report moderate or greater levels of symptoms." Premenopausal women may have an even higher incidence of side effects. How this will affect their compliance with a long-term, preventive tamoxifen trial remains to be seen.

In conclusion, while I do not have a problem with the use of tamoxifen for the prevention of breast cancer in the older, higher-risk patients, there is an obvious ethical problem when we submit healthy women of child-bearing age, who have a nil to slightly increased risk of breast cancer, to a known carcinogen which, in addition to increasing their fertility, is also a demonstrated teratogen. This is especially problematic when they are forbidden the most effective forms of birth control and are not advised to have routine endometrial exams. These risks are compounded by the possibility of an increased incidence of hepatocellular carcinoma and estrogen receptor-negative breast carcinoma, as well as a significant probability of developing ocular toxicity or thrombophlebitis.

Clinicians who are advising patients interested in enrolling in this study would do well to acquaint themselves with the available literature on the toxicity of tamoxifen, some of the most impressive of which has been published since the latest protocol was completed. In this way they may persuade both themselves and their patients that prudence in entering this trial is well-warranted.

ACKNOWLEDGEMENTS

I would like to express my appreciation to Hazel Cunningham for making me aware of the recent literature regarding tamoxifen, and to Ann Kelminski for supplying me with the NSABP Protocol.

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(Continued on page 102) ➤

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Tamoxifen: A caveat on the pro side of the debate

Virginia M Pressler MD*

Thank you for the opportunity to respond to Dr. Steven Moser's extensive letter-to-the-editor regarding the National Surgical Adjuvant Breast/Bowel Project Breast Cancer Prevention Trial (NSABP Protocol P-1), also known as BCPT.

Dr. Moser's letter is obviously written out of concern for the safety of participants in this trial and his concerns are deserving of a response. The NSABP P-1 (BCPT) study has been under discussion and development since 1984. All of the concerns mentioned by Dr. Moser have been fully evaluated by the FDA, the National Institutes of Health (NIH), the NSABP and many other groups. At a recent congressional hearing, the Director of the NIH, Dr. Bernadine Healy, described this study as one of the most thoroughly reviewed protocols ever at the National Cancer Institute (NCI)¹.

Let me address each of Dr. Moser's individual concerns about this trial.

1. Level of Risk of the Participants: Contrary to the comment that premenopausal women eligible for this study "have a nil to slightly increased risk of breast cancer," women age 35 to 40 are required to have at least a 9-fold increased risk of breast cancer compared to a population of women without these risk factors before they can be considered for this trial. Most of these women are at an even higher than 9-fold increased risk, and many live in fear of dying from breast cancer. Most of these younger women have had at least 2 first-degree relatives (mother or sisters) diagnosed with breast cancer and some have seriously considered having bilateral prophylactic mastectomies in an attempt to prevent this dread disease. This is not a low-risk population and the fear of developing breast cancer is not a trivial concern in these young women's daily lives.

The NSABP already has randomized more than 5,200 women to tamoxifen or placebo in this trial as of December 1992. Only 4% of the women so far randomized have a risk of developing breast cancer equal to that of a 60-year-old woman. Over 70% of the women of all ages randomized to date have at least a 5-fold increased risk compared to that of a 60-year old woman and those who are premenopausal on the trial have much higher risks than this.

2. Level of Reduction in Incidence of Contralateral Breast Cancers: Contrary to Dr. Moser's claim that this effect may be overestimated, more recent publications than those referenced by Dr. Moser representing 41,000 woman-years of tamoxifen treatment unequivocally demonstrate tamoxifen's

ability to reduce the incidence of recurrent ipsilateral and new contralateral breast cancer^{2,3,4}.

Furthermore, Peto's recent meta-analysis of all randomized studies demonstrated a 39% odds reduction in contralateral breast tumors in patients taking tamoxifen⁴.

3. Uterine Cancer Risk: It is not surprising that tamoxifen might increase the risk of uterine cancer due to its estrogen-agonist effect. The BCPT consent form states:

"An increased risk of uterine cancer has been reported with the use of tamoxifen. Existing data from several large controlled clinical trials using 20mg tamoxifen shows that 9 out of 3,097 women on tamoxifen developed uterine cancer (0.3%) versus 4 out of 3,091 women not treated with tamoxifen (0.1%)."

Seven randomized trials of tamoxifen all show the same relative rates of uterine cancer. It should be noted that 35% of the more than 5,000 women randomized so far on the BCPT have had hysterectomies. Thirty percent of the women under age 50 who are on the BCPT already have had hysterectomies for benign uterine changes. For those who haven't had hysterectomy, uterine cancer is rare under age 50.

All women on the study are required to have a complete pelvic exam before entry on the trial and at least annually thereafter. The patients and their gynecologists are advised to immediately evaluate any abnormal uterine bleeding and endometrial biopsies are recommended for irregular bleeding.

In the NSABP B-14 study, all of the uterine cancers that developed were diagnosed at Stage 0-1.

4. Hepatic Cancer Risk: The 2 liver cancers mentioned by Dr. Moser are the only 2 documented cases of liver cancer in the world in spite of 20 years of tamoxifen use in women with breast cancer. These 2 cases were from a Swedish trial using 40mg a day of tamoxifen (twice the currently used dose). Both of these cases occurred within 15 months of starting tamoxifen therapy. No other cases have been documented in spite of tracking thousands of women by the National Cancer Institute and the FDA.

Although liver cancers have been produced in rats given tamoxifen, this has not been reproducible in any other species. A recent paper by Mani and Kupfer⁵ examining activation of tamoxifen to reactive metabolites in microsomes, implied that the human liver is apparently much less active than the livers of rats in activating tamoxifen to reactive intermediates.

A recent publication by Han and Liehr⁶ cited by Dr. Moser describes the formation of covalent DNA adducts in Sprague-Dawley rat livers after high doses of tamoxifen. These adducts do not necessarily equate with DNA damage, which was not the subject of the investigation and no mutations were reported since

* PI, NSABP P-1
Breast Cancer Prevention Trial
Submitted for publication February 1993

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rats were sacrificed 4 hours after 1 to 6 daily doses of tamoxifen (intraperitoneal tamoxifen 20mg/kg/day on days 1, 3, and 6). The significance of this phenomenon has been the subject of research by Liehr et al since 1985^{7,8}.

In several experimental animal systems, estrogen exposure previously has been observed to result in the formation of DNA adducts. A wide range of estrogens can participate in the process, including natural endogenous estrogens. Adduct formation occurs between DNA and an unknown estrogen-induced DNA reactive compound. The experimental process is observed in liver and kidney. The details and significance of the reaction process remain a research issue. It is thought that these adducts can be stripped from DNA by normal repair processes.

Two thousand women in 7 major adjuvant randomized clinical trials using 20mg of tamoxifen have an overall median follow-up of 80 months, extending as long as 135 months for some groups. There have been no reported cases of liver cancer. A small group of 43 patients at the University of Wisconsin continued receiving tamoxifen indefinitely following completion of adjuvant chemotherapy for early stage breast cancer. Follow-up currently exceeds 11 years with no reported cases of primary liver cancer⁹.

Dr. Moser claims the tamoxifen breast cancer prevention trial does not call for specific liver function testing. This is not true. Liver function tests must be drawn on each patient before initiation of the trial and then at 3 months, 6 months, and then every 6 months for the duration of the study.

Dr. Richard Love at the University of Wisconsin has studied adverse effects of tamoxifen for many years and believes that "the much discussed possibility of human primary liver neoplasia consequent to long-term tamoxifen treatment does not deserve listing" as an adverse effect¹⁰.

The potential risk of hepatic cancer is mentioned in the BCPT consent form and is discussed with every patient.

5. Risk of Pregnancy: All women on the trial are advised of the possibility of teratogenic risks of tamoxifen to the fetus. All women are told they must avoid

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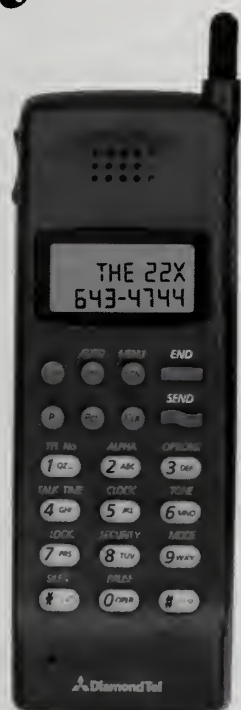


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pregnancy. Furthermore, new policies will require that all premenopausal women who could become pregnant must either have a negative pregnancy test at the time of initiating the trial or start the trial during their menstrual period. They are advised that tamoxifen can increase fertility and that adequate barrier contraceptives must be used. Again, it should be noted that 30% of the premenopausal women in this study have already had hysterectomies.

If any woman should become pregnant while on the study, her medication will be immediately stopped and the code broken so that she will know if she was taking tamoxifen.

Premenopausal women have been denied participation in clinical trials for many years because they might become pregnant. If they are denied participation in this trial, we will never know whether or not tamoxifen may benefit this large group of women at risk for breast cancer. The National Cancer Institute agrees that to exclude premenopausal women is discriminatory. Furthermore, it is demeaning to assume they cannot responsibly avoid pregnancy when they have been advised of the risks.

NSABP B-14 data suggests that tamoxifen may actually be more effective in preventing second breast cancers in premenopausal than in postmenopausal women. Furthermore the risks of deep venous thrombosis and endometrial cancer as an adverse effect of tamoxifen are rare in premenopausal patients. It would be wrong to exclude these women from the opportunity to participate.

6. Risk of Promoting Hormone-Independent Tumors: The NSABP is aware of the data in rats showing development of rapidly growing hormone-independent tumors. In humans, we do not know if the breast cancers that are prevented are the hormone-dependent tumors, but we do know that multiple, large, randomized trials have shown benefit in disease-free survival and overall survival in patients with hormone receptor-negative, as well as hormone receptor-positive tumors, treated with tamoxifen. The role of tamoxifen in hormone-independent tumors currently is being evaluated in NSABP Protocol B-23 and other studies.

Dr. Moser also comments that tamoxifen may simply delay the onset of hormone-sensitive tumors. This does not seem to be the case since continued follow-up of disease-free survival and overall survival in patients with breast cancer treated with tamoxifen shows the curves to continue to widen over time, showing prolonged benefit of tamoxifen even many years after it has been discontinued.

7. Thrombophlebitis and Ocular Toxicity: Contrary to Dr. Moser's claim that these potential toxicities are not mentioned to patients, they both are included in the consent form.

Thrombophlebitis very clearly is described as an adverse effect of tamoxifen. Women with a prior history of deep venous thrombosis or embolism and women taking coumadin or heparin are not eligible for the study.

In the NSABP B-14 study, 3 of 1,414 women receiving placebo (0.2%) versus 18 of 1,403 women receiving tamoxifen (1.3%) developed deep venous thrombosis or embolism and 2 deaths occurred. This is clearly stated in the consent. Most of the thromboembolic events were in women over age 60 and most of the affected women had a history of thromboembolic problems. These women are excluded from this study. Also it should be noted that these data are from women who all had cancer and are

known to be at increased risk of thrombosis.

Rare ocular side-effects have been reported in patients receiving tamoxifen for breast cancer. These usually consist of retinopathy with fine, white, refractile opacities located superficially in the retina and concentrated especially in the macular region. Cases of optic neuritis also have been reported¹¹.

Because of the rarity of the event, the true incidence of retinopathy has not yet been estimated accurately. The NSABP currently is planning a cross-sectional investigation of a subset of patients from protocol B-14 in order to determine the prevalence of retinal and other ocular toxicities associated with long-term, low-dose tamoxifen administration. As of August 1992, women with a history of macular degeneration of the retina are excluded from the BCPT. Tamoxifen is not known to accelerate pre-existing macular degeneration; however, the natural history of the disease is unpredictable.¹¹

Participants are questioned on initiation of the study and at 3 months, 6 months, and then at six-month intervals regarding subtle visual changes. More than a simple ophthalmoscopic exam is necessary to identify this rare ocular toxicity and, therefore, would be prohibitive to screen in every participant. Participants who do note any visual changes are referred for ophthalmologic exam. In the meantime, the cross-sectional study of the subset of NSABP B-14 patients will be forthcoming to identify the true risk level.¹¹

8. Benefits of the Study: What Dr. Moser fails to note in his letter is the potential beneficial impact of this study which far outweighs any potential risks. All medications have some side effects. Cholesterol-reducing drugs and aspirin are other examples of medications that are widely used to treat patients prophylactically to reduce their risk of disease. According to personal communication by Dr. Leslie Ford of NCI, tamoxifen has been considered by the National Cancer Institute to be at least as safe as these drugs and as safe as routine vaccinations.

It is hoped that tamoxifen in this prevention trial will be shown to reduce the incidence of invasive breast cancer by at least 33% and the incidence of myocardial infarction by 20%. Studies also suggest that tamoxifen may delay or prevent bone density loss in postmenopausal women.

I personally know of physicians already prescribing tamoxifen to healthy women at increased risk of breast cancer outside of a clinical trial. This is the real risk, and if this practice becomes more prevalent, we will never know the true relative risks and benefits of tamoxifen. Only through a well-controlled prospective study such as the BCPT can we address the risks Dr. Moser is concerned about. Only through such a trial can we identify those groups of women who have the greatest net benefit from tamoxifen therapy.

The National Coalition for Cancer Research (NCCR) supports the BCPT and states "The NCCR believes" that the bad press about tamoxifen is "sensationalistic...and represents a disservice to the women of this country... There is ample scientific evidence to support the conduct of the study. Women deserve the right to choose whether or not to participate"¹².

Tamoxifen is a relatively safe medication that potentially could make an enormous impact in saving women's lives. No medication is without side effects but the safest way to determine the relative benefits and risks is through a well-designed, controlled, clinical trial. To exclude women under age 50 from this trial, or to prescribe tamoxifen off protocol, will eliminate the

(Continued on page 98) ►

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Extraction of Lipomas: A simple technique

Greg F Reinking MD*
F Don Parsa MD*

Benign lipomas are among the most common subcutaneous fatty tumors. They are often solitary, more common in women and occur frequently during the fourth and fifth decades. They usually involve the posterior neck, back and thighs, and the great majority are less than 2 cm in diameter. Malignant transformation is extremely rare, and they usually do not require treatment. However if removal is desired, surgical excision is curative. In this article we present a simple method of resecting large lipomas measuring 4 cm to 10 cm in diameter.

Material and Methods

Twenty three patients were evaluated in this study with lipomas measuring 4 cm to 10 cm with a mean diameter of 5.5 cm. All patients were operated on in an outpatient office under local anesthesia, without any intravenous sedation.

Anesthesia was obtained by infiltration with 0.5% Xylocaine mixed with 1:200,000 Epinephrine. In order to maximize the vasoconstrictive effect of Epinephrine, 15 to 20 minutes were allowed to elapse before making a 1.5 cm to 2 cm skin incision either over the fatty tumor or at its periphery. A Kelly clamp was introduced through the incision and by opening and closing the jaws the fatty tissue was broken down while the tumor was squeezed firmly at its base toward the opening. (See Figure and Drawing 1.) This allows gradual extraction of the lipoma with very minimal bleeding. The wound was closed with interrupted 5-0 or 6-0 nylon sutures and dressed with a compression dressing for 24 hours. No limitation in activities was required and at the end of this period the patient was allowed to remove the dressing. Sutures are removed 5 to 7 days later.

Results

The 23 patients who were treated by this technique were followed over a period of 6 months. Mild ecchymosis was noted in all patients; there were no hematomas or infections. The incisions healed *per primam* and the scars were acceptable.

Two patients developed mild degrees of hypertrophic incisional scars but these did not require further treatment. Ninety percent of patients experienced none to minimal post-operative pain or discomfort. Only 12% of patients used the Tylenol with Codeine No. 3 prescribed for them.

Summary

During the past decade liposuction has been described as a desirable technique for removal of lipomas¹⁻⁴. However, this requires special, costly equipment including suction apparatus and cannulae. The method of extraction of lipomas measuring 4 cm to 10 cm as described in our series was found to be simple, fast, and free of morbidity. It can be performed in an office setting. This method avoids cumbersome and costly instrumentations that are required with the liposuction technique.

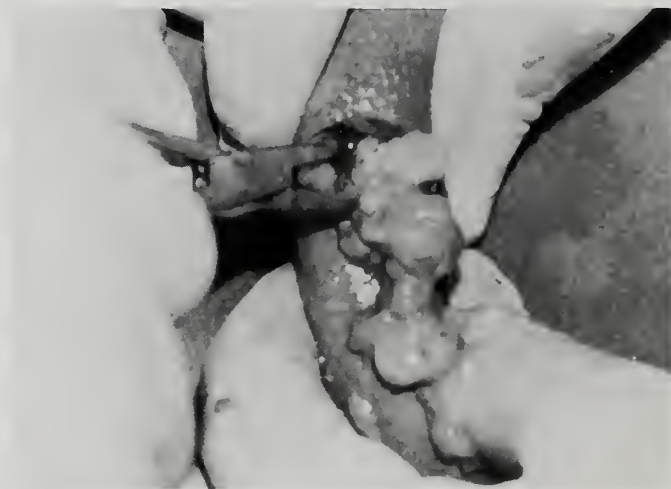


FIGURE 1.
Photograph and drawing illustrate the squeeze-extraction technique as described in the article.

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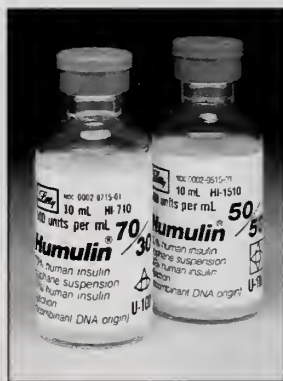
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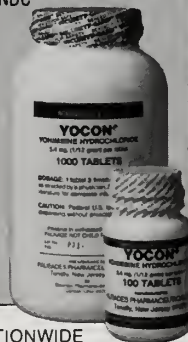
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

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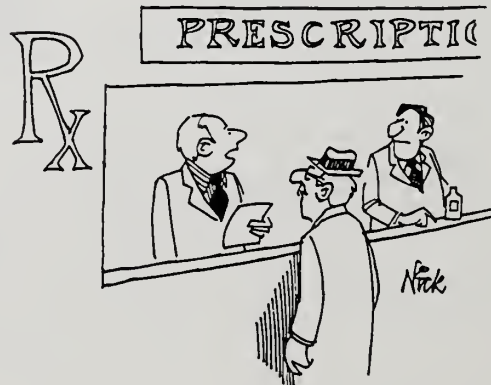
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possibility of ever determining the real relative risks and benefits in this age group. These are the women who may have the most to gain in absolute reduction of incidence of breast cancer. The known risks are well explained in the consent. How can we *not* do this study? If we do not complete this study, women will be treated with tamoxifen empirically and the risks never will be really known. Also, they may not be followed as carefully as they are on the BCPT.

The facts speak for themselves, and it must be concluded that the tamoxifen breast cancer prevention trial is one of the most important, well designed and safest studies ever conducted.

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Incredible as it may seem, that's Charlie with me at the gateway to Tirlan in Bashkiria at the southern tip of the Ural mountains in Russia on May 22, 1992. We were attending a conference about 100 miles east of Tirlan in Chelyabinsk, Siberia, the locale of the Soviet nuclear weapons complex, on the medical and environmental effects of pollution by radiation similar to what's happened at Hanford, WA in the United States.

We came home on the Trans-Siberian Railway, covering about 4,500 miles in 5 days, to Khabarovsk in Russia's Far-east, then by Aeroflot to San Francisco.

Never in my wildest dreams had I ever thought to return to my birthplace 72 years after Papa, Mama, Eric and I escaped from the Bolsheviks, traveling on the same TSRR, and came to Hawaii thanks to the American Expeditionary Force American Red Cross, the latter under Riley Allen and Arthur Jackson MD!

Hors de Combat Road Block to Health Care?

Gene Nakamoto MD in a letter to the editor expressed his feeling that the Honolulu Marathon is a roadblock to health care for East-Honolulu residents. "As a physician I am concerned for the health and well-being of East Honolulu residents who perhaps postpone medical treatment on "Non-911" medical situations, which then eventually become 911 emergencies. The medical and legal ramifications are endless...The City & County of Honolulu probably realizes some financial gain from sponsoring the marathon, but I hope we never put a sporting event above human life and well-being". (Ed: Wot rot! Such tirade for one Sunday morning a year? His colleagues certainly do not share his sentiments.)

Crisis In Mental Health Facilities For Adolescents

In Honolulu, Dennis Mee-Lee, Castle Hospital's psychiatric head, reported that the hospital will close its state-funded residential treatment program for adolescents because of an expected 20% to 25% budget cut in its \$800,000-a-year program.

Po'ailani, a private community-based shelter for disturbed adolescents closed because of a 75%

funding cut. *Kahi Mohala*, a private psychiatric hospital, will take over from Castle.

On Maui, psychiatrists are protesting the lack of facilities for children with severe mental health problems. Sally Connolly, staff psychiatrist for "The Children's Place" (a Dept of Health outpatient facility), resigned citing inadequate support and facilities. Royal Randolph, Maui Memorial psychiatric department head, reported that 3 child psychiatrists left the staff to limit their liability for assuming the care of adolescents needing hospitalization.

Gov. Waihee has promised to divert funds from other state programs to address the crisis in mental health services for adolescents.

Elected, Appointed, & Honored

Psychiatrist and 3rd-year law student, George Bussey of Kailua, won the grand prize worth \$5,000 in a Federation of Insurance and Corporate Counsel Foundation annual essay contest. His paper titled "Mental Stress Claims and the Workers' Compensation System: An Analysis of the Problem and Suggestions for Change" will be published in the Foundation's quarterly. In January, urologist John Edwards replaced pathologist Drake Will as VP of Medical Staff Services at QMC. John has been in private practice since 1974 and served as Chief of Surgery for the past 4 years. Drake will remain as a Queen's consultant.

Quiet, reticent Kailua OB/Gyn Charles Yamashiro was honored at a Castle Medical Center quarterly meeting in January. Charley was retiring after 30 years on the staff and a record 14,602 deliveries.

National News...

Limits on Malpractice Awards: On Nov 16, the Supreme Court, with one dissenting vote, upheld a Missouri law that limits the amount of money paid to medical malpractice victims (A girl was left blind and brain damaged by an anesthesia error). The justices have left intact similar laws in California and Idaho which limit malpractice awards.

Oncology Dialogue

Colo-rectal surgeon Ronald Wong presented a 41-year-old woman who had a Stage Ia left ovarian tumor resected in Dec 1991. A year later she developed an anal lesion (cloacogenic Ca) and a second tumor of her sigmoid colon which was adeno Ca on biopsy. The CA 125 was normal. CT scans of the abdomen, pelvis and chest were negative. Moderator Lois Mastrofrancesco initiated the discussion: "We probably have a salvageable adeno Ca..." Ken Sumida intoned, "Negative CT of the abdomen; C 125 normal...And fluid in the cul de sac". Pathologist Larry McCarthy reported, "The second lesion in the colon is probably mets from the ovarian Ca. The anal lesion is different." Radiotherapist Charley Yamashiro offered, "Chemo and implants after surgery." Lois commented, "We have 2 elements to treat; this is a toughie." Pathologist Grant Stemmerman added to the problem: "The lesion in the sigmoid is not necessarily metastatic. She has extensive endometriosis so it may be endometrial Ca." Radiotherapist Thanh Huynh in trying to avoid an A-P resection suggested: "Treat the anal and sigmoid tumors with radiation; then treat the ovarian Ca with chemo."

After much discussion with others joining in the melee, Ken Sumida decided: "We'll go for the home run...Do an A-P resection, debulk the tumor

and hit with chemo." Lois declared sagely: "The quality of life is very important only if you have a life."

Oncology Dialogue II

Internist Roger Kimura presented a 53-year-old man who had noticed a non-tender testicular mass 2 months earlier. Alpha fetoprotein and HCG levels were normal. The patient did not smoke or drink. CT scans of the chest and abdomen were negative. A LT radical orchiectomy was done and the pathology report confirmed a seminoma. Radiologist Howard Arimoto described the CT scan which showed small periaortic nodes. Pathologist Larry McCarthy described the pathology: "The specimen was twice the normal size and grossly a homogeneous light-tan, lobulated mass. Microscopically, it is homogeneous and cellular...The tumor markers Alpha Feto and HCG were negative".

Moderator Ken Sumida turned to oncologist Jonathan Cho: "Can you comment on preop staging." Jonathan: "Staging is helpful. Staging includes CXR, CT scans of the abdomen and pelvis." Radiotherapist Lois Mastrofrancesco interjected, "Lymphangiograms are most helpful". Chemo-therapist Dennis Wachi objected, "Let's ask the radiologist if lymphangiograms are helpful". Howard lived the discussion: "I'm not sure they're helpful". We can see nodes on the CT scan. Besides, it is a logistic problem. Lymphangiograms are a lost art. The younger radiologists are not exposed to lymphangiograms and the older radiologists have a problem with their eyes." Lois pursued her logic: "The reason for lymphangiograms is that the stage has not been determined. It may be a Stage II. It may be my own bias. And lymphangiograms are available in Hawaii. If it is Stage II, a higher dose of radiation is indicated. Fellow radiotherapist Thanh Huynh explained, "Normally we give 2000 to 2500 rads and 500 more rads if it is a higher stage. Lois interjected, "Where I trained, every patient had lymphangiogram." Thanh added: "Stage I with radiation is a 95% survival with no side effects; Stage II survival is 15% to 20%." Ken Sumida tried to soothe feelings with: "If you are to have a malignancy, this is the one to have." Pathologist Grant Stemmerman suggested a more practical approach: "Back to basics. The response to chemotherapy is so good why worry whether it is Stage I or II. Why not wait till there is recurrence". Ken concluded, "It is a judgment call. Get CT of chest and give chemo for recurrence".

Excerpts From Stitches

(The Journal of Medical Humor November-December 1992)

This is True?!

by Ralph Slonim, Miami, Florida

The receptionist told me my next patient was a gentleman who was concerned about his increasing girth. As I entered the examining room, I remarked, "If I saw that belly on a woman, I'd say she was pregnant."

"That's right, Doc," he answered. "It's been on a woman, and she is pregnant."

"My stomach has gotten so big," he went on, "that I can hardly see my penis. What do you think I should do?"

"Why don't you diet?" I asked.

He thought this over for a moment, then said, "I'll give it a try. What color would you suggest?"

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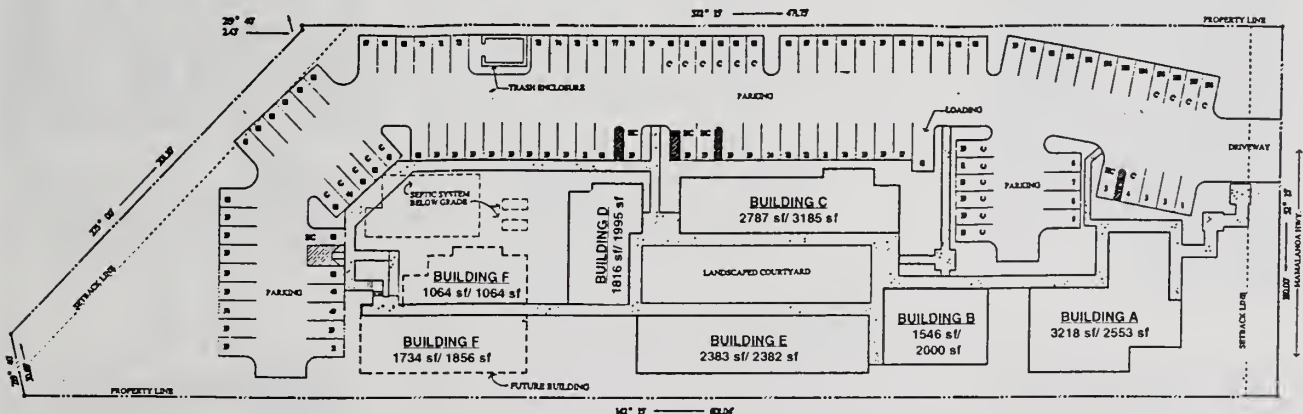
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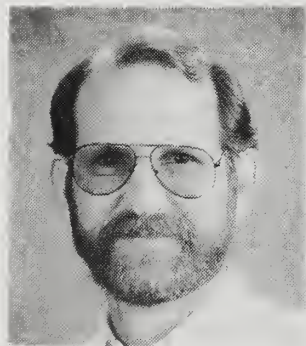
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TAMOXIFEN: CON SIDE

(Cont'd from page 88)

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol*. 1991;14:146-151.

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CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation: Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.** Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with placebo.

Digoxin: In a crossover trial involving 16 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a \geq 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vesiculocellular Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 80 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagenesis tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/– mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

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Mahalo to Dr. Norman Goldstein
and the Hawaii Dermatological Society for
all of their hard work in producing the May
issue of the Hawaii Medical Journal.

-Keith Tonaki, M.D., FCAP

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Skin Cancer/ Melanoma Month of May 1993

We did it!

On rather short notice, but stimulated by HMA Publications Committee member Norman Goldstein, the *Journal* has succeeded in coming out with a special issue devoted to the subject of skin cancers and melanomas.

Norm has done a great job of assembling manuscripts authored by an interesting variety of people in our community

— physicians and nonphysicians alike.

Nine years ago, Norm put in a great effort in a special issue to honor Harry Arnold Jr, Hawaii dermatologist of world renown and editor for 40 years of the *Journal*.

We salute Norman Goldstein MD, FACP, Hawaii dermatologist and guest editor of this issue.

Practice Safe Sun-Hawaii

When the American Cancer Society Hawaii Pacific Division asked me to serve as the 1993 Honorary Chair of the Neighborhood Education Campaign, I politely responded with a "Sorry, I can't; I'm just too busy." Then, when a busy attorney and long-time ACS volunteer, Jacqueline Earle, and a busy oncologic surgeon and chair of the ACS Hawaii Pacific Division, Scott Hundahl MD, again asked me — I just had to say "Yes."

After promoting prevention, early diagnosis and treatment of skin cancer, melanomas and wrinkles in Hawaii for almost 30 years, I felt I *must* help the ACS this year. Since the ACS had 10,000(!) volunteers ready to go door-to-door and business-to-business to distribute information and sunscreen samples to Hawaii residents and tourists, all I had to do was offer some expertise, get some people together and obtain some sunscreen samples.

And, we're off and running!

The American Academy of Dermatology has sponsored free skin cancer screening clinics in all states for 8 years. The Hawaii Dermatological Society, with the assistance of plastic

surgeons and other physicians, has been doing these clinics for 15 years — usually in churches, school cafeterias — any place that would take us and provide parking.

This year, Liberty House was kind enough to offer each of its Oahu and Neighbor Island department stores for the free skin-cancer clinics in order to reach a larger statewide population. The ACS arranged for scheduling of the clinics and had hundreds of volunteers help the dermatologists do the screenings, distribute sunscreen samples and educational materials.

Dermatologist Randy Mita ("Doctor POG") came up with a novel promotional idea: the Skin POG (milk bottle cap). Milk bottle caps are the biggest rage ever — even bigger than Pet Rocks and Rubik's Cube. The "Practice Safe Sun — Hawaii" POGs have proven to be so popular that the initial 35,000 produced were not enough to supply our youngsters' demands. Great way to get children to use sun protectives daily.*

Movie and TV star and part-time Hawaii resident Tom Selleck is also the Honorary Chair of the National Skin

(Continued on page 110) ►

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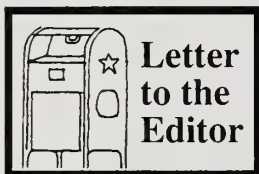
Cancer Foundation. Tom has helped to promote the "Hats in Hawaii" campaign to encourage the use of wide-brimmed hats and UV-protective garments and did some public-service announcements for the campaign.

The Skin Cancer Foundation and the Sun Protection Foundation, major national educational organizations, have provided brochures, videotapes and slide presentations to help train the 10,000 volunteers.

Students and friends of the John A Burns School of Medicine have helped at screening clinics over the years, and at the Liberty House skin cancer clinics, as well as health and fitness fairs at Blaisdell Center, Thomas Square Park and at the University of Hawaii.

With the leadership of Bruce Miller MD and Scott Bogle of the Hawaii Global Change Education Project of the Sea Grant Extension Service, we organized a Sun Awareness Steering Committee to help coordinate our programs. Miller and Bogle were instrumental in getting the first ozone laws in the country passed right here in Hawaii. Their "Hole Story"

* Thanks to an educational grant from Glaxo Dermatology, a division of Glaxo Inc. and Pam Felix, "Dr. POG" produced 100,000 for our program.



The John A Burns School of Medicine (JABSOM) applauds the *Hawaii Medical Journal* in its special issue which deals with melanoma and skin cancer. This malady is of interest to all of us who live in Hawaii because the incidence of all three forms of skin cancers (basal and squamous cell cancer and malignant melanoma) continues to increase at an alarming rate.

The Dermatology Division of JABSOM, with the collaboration of the members of the dermatologic community and the Cancer Research Center of Hawaii, is committed to dermatologic education. The objectives of the Division are threefold: 1. to provide a basic core curriculum of clinical dermatology to medical students, 2. to offer an opportunity for clinical rotations in dermatology to medical residents in hospital clinics and private offices, and 3. to conduct continuing medical education courses and seminars in the advancing fields of dermatology to practicing community physicians, allied health care personnel and the general community.

The core curriculum in dermatology includes an introduction to the basic structure and function of the skin, general patterns of dermatopathology, and identification of common dermatologic diseases. The emphasis in clinical dermatology is on those skin diseases most likely to face primary care physicians. In addition, a block of time is devoted in the

The Hawaii Plastic Surgery Society membership applauds the editorial board of the *Hawaii Medical Journal* for focusing on the melanoma/skin cancer problem.

The past several decades have seen an alarming increase in malignant melanomas and other skin cancers. Thirty-two thousand new melanoma cases in the U.S.A. with 6,800 deaths are estimated to occur in 1993 (data from NCI SEER program). Seventy new cases and 20 deaths are estimated in Hawaii alone. Fortunately, there has been a concomitant

booklet has had many printings.

The Cancer Research Center of Hawaii, the Hawaii Tumor Registry and the Queen's Tumor Registry were very supportive and supplied data on melanoma in Hawaii. Because of this data and data from private practice, we are now very aware that melanomas and other skin cancers occur in all races, not just the fair-skinned Caucasians.

Paul Berry at Punahou School started a very unique program to increase student awareness of the dangers of excessive sun exposures and the need for sun protection. This model program will be provided to other schools, private and public.

Finally, my personal mahalo to the American Cancer Society volunteers, Alice Vinton ("Vinton Volunteers"), to the dermatologists and other physicians, to Donald Onasch and Liberty House, to the staff of the Hawaii Medical Association, to Fred Reppun MD, Editor, and to the staff of the *Journal*, the contributing authors and advertisers who made this special issue possible — Mahalo and "Practice Safe Sun—Hawaii!"

Norman Goldstein MD, FACP

Guest editor, special issue on melanoma/skin cancer

Problem-Based Learning format to acquaint medical students about the basic principles of photobiology. The areas of emphasis include an understanding of the ultraviolet light spectrum, the acute and chronic effects of ultraviolet light management of skin diseases. The concepts of photoaging and photoprotection are introduced. Important attention is focused on skin cancers.

The dermatologic community is credited for their annual voluntary Cancer Screening Program which has resulted in early detection of numerous skin cancers and melanomas. In addition, the Cancer Research Center of Hawaii has helped to track the incidence of melanoma in Hawaii and together with the physicians of the dermatology community, offers updated diagnostic and therapeutic guidelines for practicing physicians in Hawaii.

JABSOM will continue its efforts to train and educate future physicians in the care, treatment and research of dermatological conditions. With well-trained professionals and an enlightened community, Hawaii indeed will be the best place to live on this earth.

Christian L Gulbrandson MD

Dean

John A Burns School of Medicine
University of Hawaii

improvement in 5-year survival rates (60% in the 1960s to 80% in the 1980s). Better understanding of the biological behavior of melanomas, particularly in regard to tumor thickness and levels of invasion, have helped to outline more logical and effective treatment plans.

However, the improved survival rates probably to a great extent can be attributed to earlier detection of the cancers. Treatment of advanced melanomas remains challenging and controversial. Therefore, early recognition and prevention of

(Continued on page 113) ►




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LETTERS TO THE EDITORS

(Continued from page 110)

melanomas and other skin cancers remain the primary goals for continuing education of the public and health care community.

Katsuji Kubo MD
President
Hawaii Plastic Surgery Society

Yes, it is possible to have fun out of the sun in Hawaii. In recent years, the mass media have repeatedly echoed the concern of dermatologists and ophthalmologists about the dangers of overexposure to the sun. It is now clear that the American public has taken note. With the ozone thinning, the problems are going to be even greater than earlier estimates indicated. Sunscreen sales have skyrocketed, people are now aware of the significance of the SPF (Sun Protective Factor), major cosmetic companies have launched "Tan without the Sun" products, and fair-skinned models now grace the covers of many fashion magazines.

In light of these recent trends, I wrote the first Oahu guidebook devoted exclusively to indoor activities in 1991 and am presently updating it again to add even more fun indoor activities. *Fun Out of the Sun/The complete guide to Oahu's great indoors* is the ideal guide for "sun smart" consumers who want to avoid or limit their exposure to the sun, particularly from 10 AM to 2 PM when the sun's rays are the most intense. This unique guidebook includes a wide range of out-of-the-sun activities, everything from visits to Oahu's most popular indoor attractions such as the Bishop Museum to offbeat diversions like ice skating, a submarine ride, or experiencing a Japanese tea ceremony. We really don't have to give up outdoor fun—just use common sense and enjoy the indoors.

The Hawaii visitor and resident of the 1990s is ready for this indoor guidebook. Existing visitor literature focuses heavily on outdoor, sunny weather pursuits. It really doesn't address the many visitors and locals who are looking for indoor activities during the hot mid-day period, or those who are already sun-burned, or the visitor and resident who is sun-sensitive. Exposed to almost constant sunshine year-round, Islanders are prime candidates for "undercover" activities. *Fun Out of the Sun's* emphasis on indoor activities makes it an excellent guidebook for rainy days too. Residents and visitors alike are often stumped for things to do during Oahu's rainy season. Visitors especially run out of ideas when the downpour lasts longer than two or three days.

All profits from the sale of *Fun Out of the Sun* are donated to Friends of Foster Kids, a non-profit organization dedicated to developing and supporting quality foster care in Hawaii. *Fun Out of the Sun* is available at book shops throughout Oahu or can be ordered by phone: 262-0071.

Christine Trecker

(Continued on page 146) ►

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The American Cancer Society Starts a Campaign

David Free*

Introduction

A Society volunteer for more than 10 years, David worked his way up through the volunteer ranks. Originally from Southern California, David majored in advertising and marketing at the University of Southern California. After moving to Hawaii 16 years ago, he became editor of the International Society of Islands.

David is Director of Production at Crossroads Press, publisher of Pacific Business News and the Hawaii Medical Journal. He has been with the company 13 years.

His review of the ACS in Hawaii follows.

*Norman Goldstein MD
Guest editor*

Volunteers in the American Cancer Society's Hawaii Pacific Division have chosen "Practice Safe Sun" as the theme for the May 1993 neighborhood educational campaign. The neighborhood campaign is an annual residential door-to-door fund-raising canvass with an educational message important to the people of Hawaii. This year many other agencies are joining the Society, making delivery of this message a community-wide program.

The American Cancer Society

The American Cancer Society (ACS) is the largest volunteer health organization in the U.S. This year the Society is celebrating 80 years of service to the nation. Back in 1913, the word cancer was rarely spoken and only 1 cancer patient in 5 could hope to live. Now, the survival rate is about 50% percent!

The Society's goals have expanded over the years and now the mission is to eliminate cancer as a major health problem by preventing cancer, saving lives from cancer, and diminishing suffering from cancer through research, education and service.

The ACS national home is in Atlanta, Georgia. From there, the national volunteers oversee operations with the assistance of a national staff.

The Hawaii Pacific Division is one of 57 divisions nationwide, providing Society services to every state, plus the District of Columbia and Puerto Rico.

In Hawaii, the ACS traces its beginnings to the late 1940s. Now, 40-plus years later, we have a roster of some 13,000 volunteers!

Local unit offices in each division provide the services for which the Society is so renowned. The Hawaii Pacific Division currently has 8 unit offices: There are 3 on Oahu, 2 on the Big Island and 1 each on Kauai, Maui and Guam. The American Samoa unit is reactivating and the Molokai branch opened an office this past year.

Service to the Community

Research, education, service and rehabilitation are the primary programs provided by the ACS. Since 1946, the Society has spent more than \$1.4 billion to find ways to prevent, detect and treat cancer. Researchers who are awarded ACS grants are among the best in the country. Twenty-five have won the Nobel Prize, 7 of them since 1986.

As a matter of policy, approximately 1/4 of ACS budgets (both at national and division levels) go to research. The Hawaii Pacific Division is very proud of the fact that nearly \$700,000 of research grants were funded for the University of Hawaii Cancer Research Center by the Society in the 1990s.

Educational efforts help the public in specific ways to lower the risk for cancer through quitting smoking, proper nutrition and limiting exposure to the sun. The ACS stresses the importance of tests for early detection of breast, colorectal, prostate and other cancers. The Society also provides up-to-date information and materials to health professionals.

Service and rehabilitation programs offer information, guidance and support for cancer patients and their families. "Angels on Wheels" is a subset that provides volunteers who drive patients to their appointments for treatment. Home care supplies and equipment are available. "Reach to Recovery," for women who have had breast cancer, is one of ACS's larger support groups.

In delivering the early detection message, cancer education programs are provided through clubs and organizations and in homes, schools and churches. We use a speaker's bureau, videos, brochures and person-to-person contact, such as the annual neighborhood educational campaign in May to disseminate these educational messages. The information reaches more people today than ever before through the news media.

As a volunteer organization, we are proud that our volunteer-to-staff ratio is among the highest in the country. In addition to providing most of the services, volunteers serve on boards of directors and standing committees at the national, division and local levels.

The Hawaii Pacific Division is especially proud that Reginald C.S. Ho MD of Straub Clinic & Hospital currently is the Society's national president.

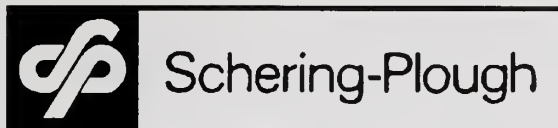
Practice Safe Sun

With the help of many similar-minded groups throughout Hawaii, we envision the Practice Safe Sun program to evolve into an on-going program to educate all residents of Hawaii. "Every BODY can get skin cancer, regardless of skin color" is the "tag-line" for the campaign. It was chosen to try to convince Hawaii residents that fair-skinned people are not the only ones who get this most-common form of cancer.

American Cancer Society volunteers asked prominent Honolulu dermatologist Norman Goldstein to work with them on the Practice Safe Sun campaign. Dr. Goldstein has advocated this message for many years and has been a valuable resource as the Society developed various facets of the program.

(Continued on page 120) ►

* President
American Cancer Society
Hawaii Pacific Division



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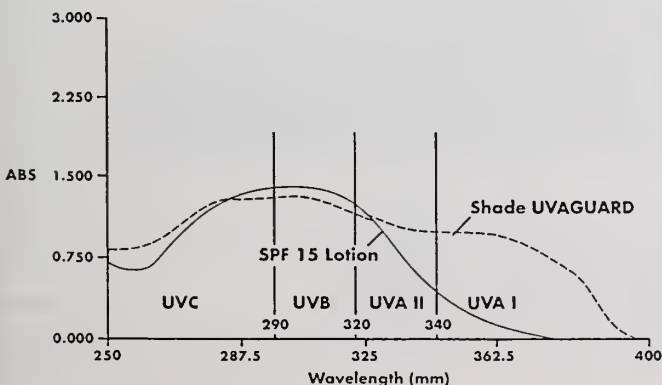
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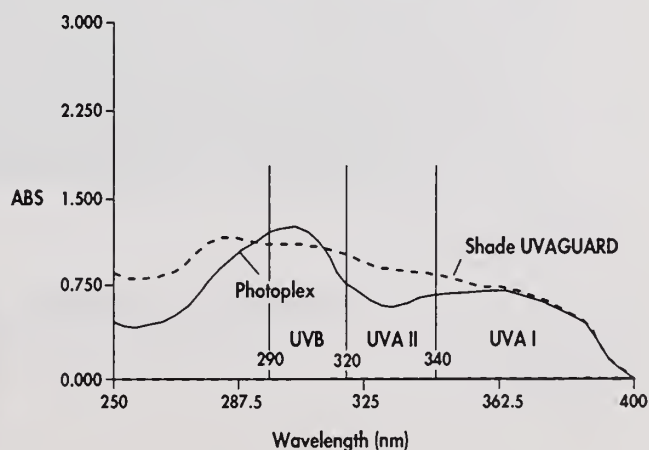


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Background

Sunlight's contribution to solar injuries and the development of skin cancer has been recognized since the beginning of the 20th century. While the photodamage spectrum traditionally has been considered as a set of conditions important for outdoor workers, it has become apparent over the past 2 decades that those who participate in outdoor recreation also are exposed to significant health risks.

The incidence of skin cancers has increased alarmingly over the past decade and forecasts anticipate an even more perilous epidemic. An important contributing factor to the epidemiologic shift of this disease has been the advent of economy-class air travel. In addition, the travel industry has furthered this outcome by advertising the "healthy tan", dismissing the warnings of dermatologists and ophthalmologists as alarmist.

In the past, concern about the negative effects of exposure to the sun focused on the UV-B wavelengths (290 to 320nm). Recently, however, it has become recognized that UV-A wavelengths (320 to 400 nm) should be monitored as well, for a more complete evaluation of sun-related health risks. Examples of this new concern already can be seen in the U.S., Canada, Europe and in other locations where sunscreens are formulated to provide UVA and UVB or broader-spectrum protection.

A heightened awareness of the risks of excessive UV exposure has been publicized through public health "safe sun" education campaigns and environmental concern over depletion of the stratospheric ozone layer. These influences together with the introduction of new UV-sensing and communications technology are in a timely position to help counter the present inattention to UV protection of one's person.

As part of the new focus on preventive medicine in the developed world, public health programs promoting safe-sun awareness are being established rapidly. It is well recognized that Australia and New Zealand have been the most active in this area, mainly the result of rapid escalation of skin cancer rates in those countries.

Two problems exist that make promoting safe-sun behavior a challenge: The invisibility of UV radiation and the often negative tone of the educational message. How people spend their leisure time is a personal and controversial subject. Whereas the public may be aware of the dangers of excessive exposure to the sun's rays, overly negative propaganda can result in undesired reactions.

Hence, 2 elements should exist in the effective delivery of a practice safe-sun message: The first is to make UV radiation a measurable entity that can be understood and related to easily. The second element is a message that has enough emphasis on the dangers of excessive exposure without presenting the sun as something to be avoided at all costs. The latter point especially is important in sunny places where people live or visit.

The problem of the invisibility of UV radiation has been overcome with the development of new technology that makes available accurate and affordable sensors to measure UV wavelengths important to the skin. This development promises to alter significantly sun-oriented attitudes and behaviors and promote personal UV protection.

Technology

The basic problem in providing accurate and affordable monitoring of the doses of UV radiation that affect the skin has been in the development of a low-cost sensor with a response that matches the reaction of the skin to sunlight. Conventional detector systems, using relatively bulky interface filter technology, provided solutions typically costing several thousand dollars.

The Environmental Monitoring Technology Ltd. (EMTEC), solution employs a miniature sensor that uses aspects of conventional semiconductor technology coupled with innovative optical technology—all at a dramatically lower cost. The response of the EMTEC sensor is closely matched to the known UVB-doses curve, including sensitivity to a UVA component, to best simulate the total effect of UV radiation on the skin. Innovative design geometry has achieved an excellent cosine correction factor which accurately detects radiation effects on the sensor from a wide range of angles. All of these features are essential for accurate monitoring of UV exposure. For these reasons, the EMTEC sensor is considered to be the founder of a new generation of UV monitoring equipment.

Applications

EMTEC's range of products incorporates its revolutionary sensor and has the flexibility to adapt to novel applications in

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Ozone Depletion: Causes, Potential Effects and Remedies

Bruce J Miller PhD

Scott P Bogle AB

The ozone layer functions as a protective screen, filtering out most of the sun's harmful ultraviolet (UV) rays. This protective layer is located in the stratosphere between 15km and 35km above the earth's surface. Ozone is actually a form of oxygen. In the lower atmosphere, oxygen atoms commonly bond with each other in pairs. This molecule, abbreviated as O₂, is the form of oxygen we need to breathe. Ozone is a more unstable and uncommon molecule made up of 3 oxygen atoms and is abbreviated O₃.

In addition to the stratospheric ozone layer, ozone also is found in the layer of the atmosphere closest to Earth, known as the troposphere. While the ozone layer in the stratosphere far above our heads protects us from UV radiation, ozone in the troposphere is harmful to breathe and damages crops and trees. Tropospheric ozone is formed by the reaction of sunlight with substances such as car exhaust and industrial chemicals and is often referred to as photochemical smog. Ozone in the troposphere provides some protection from UV rays, but its dangers far outweigh its benefits.

What is damaging the ozone layer?

The ozone layer is being attacked by man-made chemical compounds containing chlorine and bromine. The most common of these are chlorofluorocarbons (CFCs) and bromofluorocarbons (halons). Because of their stable chemical structure, these compounds don't break down in the lower atmosphere. They take 5 to 10 years to reach the stratosphere, where they are broken down by intense UV radiation¹. This breakdown releases atoms of chlorine (from CFCs) or bromine (from halons) that react with and destroy ozone. Each of these atoms is able to react repeatedly and destroy as many as 100,000 ozone molecules².

The evidence

Since 1985, scientists have been studying the ozone "hole" that forms every year over the South Pole during the Antarctic spring. Within this hole ozone levels are depleted by as much as 50% to 60%³. The size and duration of the hole continue to increase, opening earlier and closing later each year, exposing

an area larger than the United States to unusually high levels of UV radiation. In the last several years this depletion has extended to include southern Chile.

In 1991 a team of United Nations (UN) scientists found that not only is the ozone layer thinning over middle latitudes in both the northern and southern hemispheres, but that depletion is now also occurring during the summer. Up to that point, depletion had been recorded only during the colder winter months. Depletion over the United States now averages 3.5% in summer and reaches 5.5% in the winter, exceeding 5% into early June³.

In February 1992, NASA released data from its Second Airborne Arctic Stratospheric Expedition showing extremely high levels of ozone-depleting chlorine monoxide in the atmosphere over most of the northern United States, Canada, northern Europe, and Asia. Depending on weather conditions, this chlorine could cause temporary ozone loss of as much as 30% to 40% over these heavily populated areas during any given winter in the next several years⁴. The same press release reported ozone loss of up to 10% over tropical latitudes, including much of Hawaii, probably related to sulfate droplets in the volcanic plume from the 1991 eruption of Mt. Pinatubo in the Philippines. Scientists hypothesize that these sulfate droplets catalyze the destruction of ozone by chlorine⁵.

At present, predictions for future ozone-depletion over the remainder of the decade vary. At the conservative end, some scientists predict another 3% loss by the year 2000. Dr. Joe Farman, a British scientist who was one of the discoverers of the Antarctic ozone hole, projects roughly a 20% depletion over the United Kingdom and northern Europe⁶. This projection has been echoed by Dr Sherwood Rowland, one of the scientists who, in 1974, first suggested that CFCs had the potential to damage the ozone layer. Between these high and low extremes, the United Nations Environmental Programme based its studies of the impact on the environment the result of ozone depletion as a sustained average of 10%⁷.

Banning the CFCs

The destruction of ozone by CFCs was first hypothesized in the early 1970s; this led to public outcry, a ban on their use in aerosols in the United States and a temporary decrease in their emissions. However, despite knowledge of their destructive capability, the usefulness of CFCs and halons in other areas led to huge increases in production through the mid-1980s. By the late 1980s, CFC and halon use was considerably higher than it had been prior to the aerosol ban in 1978⁸.

CFCs are used widely as refrigerants in air conditioners, refrigerators, freezers and heat pumps; as blowing agents for

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some foam plastics; as solvents in the cleaning of metals and the manufacturing of electronics. Halons are used as agents in fire extinguishers in both large stationary systems designed to protect electronic equipment and in portable ones.

Other ozone-depleting chemicals include carbon tetrachloride, used primarily as a solvent; methyl chloroform (1,1,1-trichloroethane), used as a metal cleaner; and in various products such as spot removers, insecticides and shoe polish sprays. Methyl bromide has recently been found to be released by fungicides.

The United States is the world's largest producer and consumer of CFCs and halons, accounting for close to 30% of world production and use⁸. Since 1990, United States CFC production has been cut in half, but still has a long way to go. Because of their proven threat to our health and environment, we need to stop using these chemicals, and we can do this without lowering our standard of living (for information on how to reduce the use of these chemicals see the section entitled "Meanwhile what can we do?").

The alternatives

Many replacement chemicals now are available; others are being tested. Generally they are far less destructive to ozone, while being almost as efficient as those currently in use. Substitutes such as HFC-134a (used as a replacement refrigerant for CFC-12) and butane (used as a blowing agent) have no damaging effect on ozone; however, they still contribute to the greenhouse-warming effect. Many companies that used CFCs as solvents have successfully switched to alternatives, such as citrus extracts or even soap and warm water.

Refrigeration companies are developing appliances using helium, butane, and hydrogen as coolant gases. Other alternatives, such as hydrochlorofluorocarbons (HCFCs), are considered by many to be interim substitutes because their ozone-depleting potential is far lower than that of CFCs. Eventually these will need to be phased out as well, as some HCFCs may be more destructive to ozone than previously thought⁹.

Can the ozone layer repair itself?

Ozone is constantly being both created and destroyed in the stratosphere. The average life of an ozone molecule is relatively short and until recently ozone was being created at least as fast as it was being destroyed. Unfortunately, the chlorine and bromine compounds we have released into the atmosphere have altered this balance, and they are destroying ozone faster than it can be created. After emissions of these chemicals cease, the ozone layer will eventually repair itself. However, recent estimates indicate that even if we stop all CFC emissions today, depletion will continue to worsen for at least a decade before any repair can begin. For the same reason, the Antarctic ozone hole is estimated to not fully repair itself until the late 21st century³.

The effect of ozone depletion

Life as we know it on Earth developed under the protective shield of the ozone layer and has been sustained by this protection for nearly a billion years. Significant depletion of this shield will be harmful to both humans and other living things

on which we are dependent. Dangers from elevated levels of UV radiation include:

On human health:

- **Increased instances of skin cancer:** According to the United Nations Environmental Program (UNEP) *Environmental Effects of Ozone Depletion 1991 Update*, every 1% thinning of the ozone layer will result in approximately a 2.3% to 2.6% increase in non-melanoma skin cancer. This report, based on data from ongoing research by NASA and the international scientific community, predicted that a sustained 10% decrease in ozone will be associated with a 26% increase in non-melanoma skin cancer. All things being equal, this would result in an increase in excess of 300,000 cases per year world wide⁷.
- **Increased instances of cataracts, the leading cause of blindness in the U.S.:** The same UNEP report also predicted that, all things being equal, a sustained 10% decrease in ozone depletion will lead to between 1.6 and 1.75 million additional cataract cases a year worldwide⁷. UV also is associated with age-related nearsightedness and solar retinopathy, or eye burn, which can cause temporary blindness.
- **Weakening of the immune system:** Recent evidence indicates that while people with fair skin are most likely to suffer the brunt of increased skin cancers resulting from ozone-depletion, people of all skin types are at equal risk of the immunosuppressive effects of elevated UV radiation levels. Recent research cited in the 1991 UNEP report indicates that exposure to UV also can activate the HIV virus⁷.
- **Premature wrinkling, toughening and aging of the skin.**

On crops and other land plants:

- **Reduced crop yields and stunted growth of natural vegetation:** Plant groups sensitive to increases in UV radiation include beans, melons, peas, and cabbage. Soybeans, the third most important food crop in the U.S., have been found to be particularly sensitive to elevated UV levels. According to the 1991 UNBP report, a 25% reduction in ozone could cause a decrease in soybean production of up to 20%⁷.

On marine life:

- **Disruption of the marine food chain and further reduction of already shrinking fisheries:** Fish larvae and phytoplankton living near the ocean surface are harmed by exposure to increased levels of UV radiation. Phytoplankton account for 75% of marine plant mass and form the base of the marine food chain. Additionally, these organisms are important in the production of oxygen. Recent research in the Antarctic found a 6% to 12% reduction in primary productivity by marine phytoplankton, attributed to elevated UV levels under the Antarctic ozone "hole"⁹.

Aside from the studies cited above, there has been relatively little research on the impact of ozone depletion on terrestrial and marine ecosystems. While human beings can offset the effect of higher UV levels by adopting behavioral changes, this is not as easy for some other organisms to do. Increased

(Continued on page 122) ►

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THE AMERICAN CANCER SOCIETY SOCIETY STARTS A CAMPAIGN

(Continued from page 114)

Nearly 10,000 American Cancer Society volunteers will be knocking on neighbors' doors statewide in early May. At each household they will leave a kit filled with informative and attention-getting materials to emphasize the Practice Safe Sun message. The kit includes a Practice Safe Sun brochure with prevention and self-examination tips, the ABCD danger signs of melanoma, and other facts. Similar informational pieces will be used by the Society in a companion mailing to homes not reached by the door-to-door volunteers. Also to be included in the kits is a sample of SPF 15 (or higher) sunscreen. And, of course, to appeal to the younger set (not to mention their parents), each kit will contain a milk-bottle cap with the Practice Safe Sun theme.

For several years, members of the Hawaii Dermatological Society have been providing free skin-cancer screenings during May, which is national Skin Cancer Awareness Month.

This year Liberty House department stores statewide will provide space for the screenings on May 12 in a joint promotional effort. Liberty House stores hosting screenings are: Ala Moana Center, Pearlridge Center, Downtown, Windward Mall, Kailua, Kahala Mall, Maui, Kona, Hilo and Kauai.

As planning progressed this past winter and spring, many other activities were being developed. More than a dozen organizations are working together to make an impact for health on the people of Hawaii.

Summary

Dr. Goldstein has summed it up for the Hawaii Medical Association: "Because of the decrease in the ozone layer and the marked increase of melanomas and skin cancers, as well as sun-related cataracts and other environmental problems, we are very pleased that the American Cancer Society has decided to choose skin cancers/melanomas to alert our population to the dangers of excessive UV exposures."

The volunteers of the American Cancer Society hope that idea is developed and molded into something big enough to significantly reduce the incidence of skin cancer in Hawaii.

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UV radiation is also only one of many pressures, along with loss of habitat, changing climate, and introduced species, placed on organisms and ecosystems by human-induced global change. In the face of uncertainty over the compound effect of these pressures, we must take whatever steps we can to minimize depletion of the ozone layer.

What we can do

Depletion of the ozone layer is a global problem. It stands to affect all people in all parts of the world. Solving the ozone problem requires action and cooperation from world organizations, national, state and local governments, industry, and individuals.

The role of government

The U.S. is one of approximately 70 nations that signed the Montreal Protocol on Substances that Deplete the Ozone Layer. This 1987 UN treaty called for a 50% reduction from 1986 levels in CFC production and a freeze on the production of halons. In London in 1990 these provisions were strengthened to require a complete phase-out of CFCs and halons by 2000, with the elimination of methyl chloroform and carbon tetrachloride by 2005 and 2000 respectively. The 1990 revisions of the U.S. Clean Air Act call for a similar phase-out schedule, while also providing some regulation in areas not covered by the Protocol².

Since 1990, these phase-out dates have shifted in response to information provided by ongoing research. In 1992 the U.S. government followed the lead of many European countries by announcing an acceleration of the phase-out schedule for CFCs and carbon tetrachloride. Production of these chemicals now will cease by December 1995. Halon production will be eliminated in 1994. These same phase-out dates were adopted later in the year by the other parties of the Montreal Protocol, while the European Community upped the ante by agreeing to stop producing CFCs by January 1995¹⁰.

These are all important steps and should be applauded. In the coming years similar policies that are responsive to new research findings will need to be developed to address other environmental threats as well. However, we should remember that international agreements and federal regulation are only part of the solution. Until CFCs, halons and other ozone depleters are finally phased out there are other steps that can be taken to prevent unnecessary emissions of these chemicals. As was mentioned earlier, many companies are finding ozone-safe substitutes and switching over to them in advance of the dates required by law. Several state governments also have taken action. Hawaii was the first state in the nation to mandate recovery and recycling of CFCs used in car air-conditioners and to ban over-the-counter sales of the chemicals. Vermont, Oregon, Florida, Maine and Minnesota followed suit.

Meanwhile what can we do?

The 1990s have been called the decade of individual responsibility. We as individuals can make a difference with the products we use and the choices we make. When the threat to ozone posed by CFCs in aerosol sprays was first reported in the 1970s, American consumers simply stopped buying aerosols once they learned of the danger these sprays posed to

the ozone layer. This action prevented large amounts of CFCs from being released into the atmosphere and led to a government ban on CFC use in aerosol products. Here are steps that individual consumers can take today to protect the ozone layer:

- 1) Leaking car air-conditioners have traditionally been the largest source of CFC emissions in the United States. Both federal and state laws require service stations to recover and recycle CFCs when air-conditioners are repaired, but there has been little enforcement of these measures. Therefore:
 - Make sure your service station recycles CFCs before you have your air-conditioner repaired.
 - If you are buying a new car, consider a model without an air-conditioner or one using new non-depleting refrigerants.
- 2) Avoid foam containers and packaging such as foam popcorn unless they indicate that they were not made with CFCs or HCFCs. Not only do some of these contain ozone-depleting chemicals, but they are also a problem in disposal of waste. As of February 1989, most polystyrene manufacturers stopped using the most destructive CFCs, but some of the replacements, especially HCFC-22, have been found to be more damaging than previously thought.
- 3) Immediately repair any leaks in your refrigerator. If you are discarding a refrigerator, make sure the CFCs are recycled before it is scrapped. If you are buying a refrigerator, consider new CFC-free models.
- 4) Avoid purchasing halon fire extinguishers. These usually can be identified by the yellow canister. Traditional dry chemical or carbon dioxide models will work in most cases. The sale of most portable halon fire extinguishers will be prohibited in Hawaii beginning in July 1993. Call your local fire department for information; if you already own a halon extinguisher, store it until halon recycling is available.
- 5) Consider alternatives to air-conditioning in your home. If you are building a home, look into passive cooling designs. For an existing home, consider the following options:
 - Insulate to keep heat out.
 - Install a cooling system using fans.
- 6) Check all products before purchase to avoid ozone-depleting chemicals. These chemicals include: CFC-11, CFC-12, CFC-113, CFC-114, CFC-115, (The abbreviation CFC will sometimes be replaced by R for "refrigerant", i.e. R-11, R-12, R-113, etc.); Halon-1211, Halon-1301, Halon-2402, 1,1,1-trichloroethane (methyl chloroform), and carbon tetrachloride are also to be avoided.
- 7) Write to your federal, state and local government representatives and inform them of your concern about ozone depletion.

Global problems such as ozone depletion can seem huge, abstract, and impersonal, but just as we each stand to be affected by these problems, we can each make a difference. Talk about this and other global change issues with your family, friends, and colleagues, and follow the steps listed above that you as an individual can take to reduce ozone depletion.

(Continued on page 131) ►

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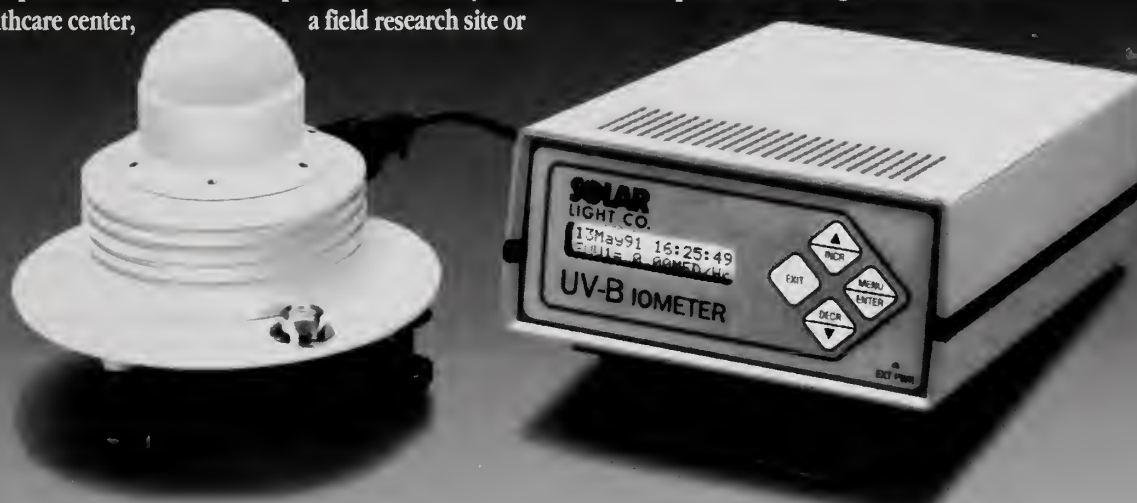
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The Gender-Related Issues in Malignant Melanoma

Darrell S Rigel MD, FAAD*

The problem of malignant melanoma is important in the United States, in the world as a whole, and particularly in Hawaii with its high levels of ultraviolet radiation. It is estimated that 32,000 Americans will develop melanoma and 6,800 will die of this tumor in 1993. Melanoma is now the seventh most frequent cancer in the United States. It is more common than ovarian, cervical, CNS cancer and leukemia¹.

Both incidence and mortality from melanoma are rapidly increasing. The incidence of melanoma has consistently increased 6% a year and the death rate has increased 2% a year since 1950. At current rates, one in 400 will die of this tumor. Should this rate of increase continue, by the year 2000, it is estimated that one in 75 Americans will develop melanoma during a lifetime. The highest melanoma incidence in the U.S. is found in Hawaii. Melanoma is increasing faster than any other cancer in the United States and all over the world².

Gender-specific epidemiologic issues

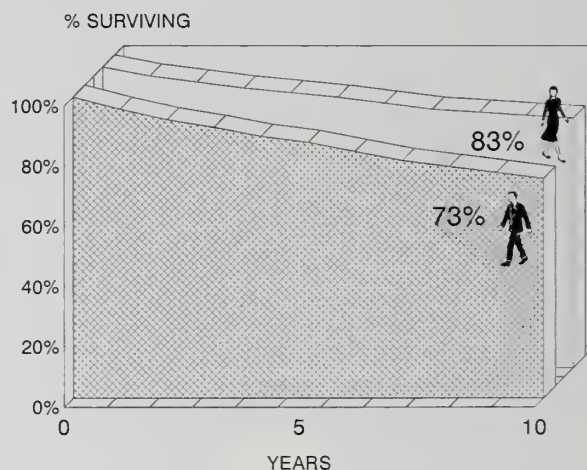
Most studies show an overall slight preponderance of men over women developing melanoma. The rate of melanoma is increasing most rapidly in persons under the age of 40. Women predominate with a 3:2 ratio from ages 20 to 29 and a 2:1 ratio from ages 30 to 39. Melanoma is currently the most frequent of all cancers in women ages 25 to 29, and second (after breast cancer) in women ages 30 to 34.

Above the age of 40, these curves cross with more men developing melanoma than women. By age 80, men outnumber women almost 2:1 in terms of developing this cancer. Similar findings are being noted worldwide. The reasons for these differences in gender-incidence are as yet unknown.

Prognostic factors

The most important factor that influences survival in persons with melanoma is how deep the lesion has penetrated into the skin. A small difference in tumor thickness can be critical. Almost all persons with melanoma less than 0.75 mm (1/32) will survive while less than half will survive when the lesion is greater than 3.0 mm (1/8 inch) in thickness. Other factors that influence survival include whether the tumor is localized or has spread (stage), if it is eroded and/or has bled (ulceration), and where on the body it is located (anatomic site).

There are significant differences in survival in men versus women who have developed melanoma. After correcting for other prognostic factors, women have a significantly improved 5- and 10-year survival over men. Data from 1,143 melanoma patients from New York University Melanoma Cooperative Group show a 10-year survival of 83% in women versus 73% in men. (Figure 1) This finding of differences in survival by gender are supported by many other studies in the United States and worldwide.



NEW YORK UNIVERSITY MELANOMA COOPERATIVE GROUP 1993

Figure 1: Comparison of 10-year survival in male and female patients. New York University Cooperative Group unpublished data.

Several reasons have been proposed for this difference in survival by gender. First, melanoma is a cancer that is hormonally influenced. Progesterone and estrogen may favorably influence in persons with this tumor. Second, men most often develop their melanoma on the upper back while women often experience lesions on their legs. The difficulty in seeing melanoma arising on the back may result in a delay in diagnosis³. In fact studies have suggested that men tend to delay seeing a physician for evaluation of a suspicious lesion as compared to women. This delay lets the melanoma progress resulting in thicker, more often ulcerated tumors that may be more likely to have spread prior to the initial visit to the doctor. These factors would also contribute to a lower rate of survival in men.

Trends in mortality for melanoma also show gender-specific findings. The overall death rate for melanoma in the United States is now 2.7 per 100,000. However, the rate in men is 3.2 per 100,000 versus 2.2 per 100,000 in women. Data from the

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The Hawaii Dermatological Society

wishes to thank the American Cancer Society for its support of educational projects warning Hawaii's population about the dangers of over exposure to the sun.

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Skin Cancers in Hawaii (1993)

Norman Goldstein MD, FACP*

Basal cell cancers are the most common of all cancers. They rarely metastasize and very rarely kill. Melanomas, however, do kill! An estimated 20 people in Hawaii will die this year from malignant melanoma. Early diagnosis and treatment can save much morbidity—surgery, scars and other defects—and can save lives. This manuscript reviews melanoma data from several agencies in Hawaii and from the experience of the author's private practice. In his private practice, he has seen the incidence of melanomas jump from an average of one a year in 1970 to 1975 to 7.4 each year between 1986 and 1990. While basal cell cancers and melanomas occur more in Caucasians, they are seen in all races. Everyone can get skin cancer and melanoma. Physicians must teach their patients to Practice Safe Sun—Hawaii.

Basal cell cancers, the most common type of all skin cancers, are not reportable to any state or national recording agency. The American Cancer Society projects more than 700,000 new cases of basal and squamous cell cancers in 1993¹.

Stone and Elpern, Hawaii dermatologists, and their associates did a very thorough study of non-melanomas on the island of Kauai between January 1, 1983 and December 31, 1983². In their review of 131 Kauai residents with non-melanoma skin cancers, 89 had basal cell cancers and 24 had squamous cell carcinomas (5 had melanomas). The ethnic distribution was as might be expected.

The authors also clearly showed the incidence of non-melanoma skin cancers on Kauai to be significantly higher than anywhere on the Mainland. The age-adjusted incidence for basal and squamous cell carcinoma was over twice that of New Orleans, 2.5 times that of New Mexico, and 5 times that of Seattle.

Dermatologists, plastic surgeons and pathologists agree that basal cell cancer is the most common of all cancers. Fortunately these rarely metastasize but do invade locally if untreated; hence, the old name "rodent ulcer." Deaths from basal cell cancers are very, very rare.

Melanomas, on the other hand, do kill. The American Cancer Society estimates 6,800 deaths from melanoma (4,200 male and 2,600 female) in 1993. They also estimate a total of 32,000 (17,000 male and 15,000 female) new melanomas will be diagnosed in the United States this year. Hawaii will have 70 of them, with 20 deaths!

Despite the fact that the number of melanoma deaths in Hawaii is relatively low compared to 425 lung cancer, 200 colon and rectal cancer, 100 breast cancer and 100 prostate cancer deaths, many of these melanoma deaths could be prevented with early diagnosis and treatment. This article will review the melanoma data from several sources in Hawaii:

- Queen's Medical Center (QMC)—Oncology Data Registry
- Cancer Research Center of Hawaii (CRCH)—Epidemiology Program
- Hawaii Medical Association — Hawaii Tumor Registry (HMA-HTR)

Between 1960 and 1961, The QMC Oncology Registry recorded 224 melanoma cases (141 male and 83 female). By far the largest ethnic group was Caucasian, 182 (81.3%); Hawaiian, Filipino and Japanese (11,10 and 9% respectively); Chinese 3 and others 9. The highest age groups with diagnosed melanoma were at 50 to 59 years (52 patients) and 60 to 69 years (55 patients). It should be noted that 4 patients out of the total were 19 years of age or younger, and 14 were aged 20 to 29 years.

The latest data available at this time at QMC indicate 4 more melanomas in the first 6 months of 1992 (2 Caucasian, 1 Hawaiian/part-Hawaiian, and 1 other). There were 3 females and 1 male. In summary, 142 male and 86 female patients were registered between 1960 and mid-1992 at The Queen's Medical Center Registry.

CRCH

LeMarchand and his associates in the Epidemiology Program of the Cancer Research Center of Hawaii have the largest data base of melanoma patients in the State. As part of

Table 1:

Ethnic Group	Basal Cell Cancer	Squamous Cell Cancer
Caucasion	80	19
Japanese	7	4
Filipino	1	1
Part Hawaiian	1	0
Totals	89	24

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their dietary studies relating to cancer, they have examined 500 melanoma patients between January 1986 and June 1992. There were 306 males and 194 females in their study:

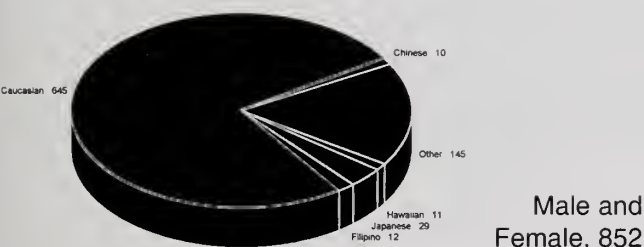
Table 2		
Ethnic Group	Male	Female
Caucasian	279	174
Hawaiian/Part Hawaiian	12	7
Japanese	8	6
Chinese	3	5
Filipino	1	2
Unknown	2	0
Other	1	0
Totals	306	194

HMA-Hawaii Tumor Registry

HMA-HTR is supported by the American Cancer Society, Hawaii Pacific Division, the Cancer Research Center at the University of Hawaii John A Burns School of Medicine and by the State Department of Health. HMA-HTR recorded 852 melanomas diagnosed between 1985 and 1991. In this 7-year period there were 527 males and 325 females. As anticipated, the majority were Caucasians (645) with 412 males and 233 females; the data clearly indicates other racial groups do get melanomas in Hawaii.

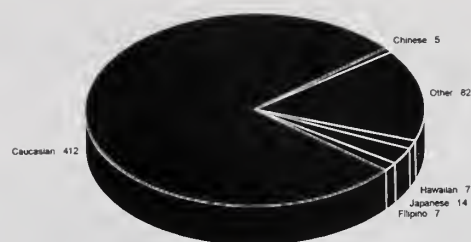
Regrettably there were 137 unknown races, but most can be assumed to be Caucasian. The complete data from the HTR include 15 different types of histologic codes for the 852 melanomas. This will be reported elsewhere.

Melanoma in Hawaii
1985 to 1991



Male and Female, 852

Female, 325



Male, 325

Two rare but very significant types of melanomas deserve special mention here: there were 6 amelanotic melanomas (5 Caucasian and 1 Hawaiian). These are melanomas without the melanoma color, ie had normal skin color.

There were also 4 acral lentiginous melanomas: 3 in Filipino men and 1 in a Hawaiian. These usually are seen on the sides of the sole of the foot in members of the dark-skinned races.

The worldwide increase of cutaneous malignant melanoma is rising faster than any other cancer³. But as Koh et al⁴ have noted, most registries record data from patients admitted to hospitals and/or from biopsies interpreted in hospital-based laboratories.

This study clearly shows that Hawaiians and part-Hawaiians are developing melanomas.

Melanoma data from a private dermatology practice

In preparation for the "Practice Safe Sun—Hawaii" campaign for the American Cancer Society Hawaii Pacific Division, we were asked to review our melanoma cases.

During the years 1972 to 1993, we practiced Dermatology in downtown Honolulu; we have always seen a wide diversity of ages, ethnic groups and occupations. We were seeing more patients with melanoma over the years but the actual data really astounded us.

Table 3:

Ethnic Group	Male	Female
1969	2	2.0
1970-1975	5	1.0
1976-1980	19	3.8
1981-1985	20	4.0
1986-1990	37	7.4
1991-1992	11	5.1

Some of these melanoma cases were diagnosed and treated by either oncological or plastic surgeons in Hawaii or on the Mainland and were referred to us for follow-up. About 80% were diagnosed in our office.

There were 56 male and 38 female patients; of the 94 patients examined, 87 still are living, 5 males and 2 females have died. As expected, the racial rainbow of skins included a vast majority of Caucasians (86); 4 of Japanese ancestry, 2 Chinese, one Latin-American and one Hawaiian.

(continued)►

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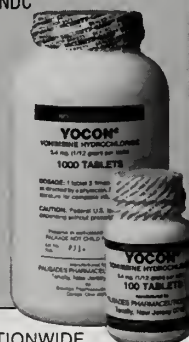
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

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SKIN CANCERS IN HAWAII (1993)

(Continued from page 127)

What Do These Statistics Mean?

According to the Skin Cancer Foundation, the death rate from malignant melanoma has more than doubled since 1950⁵. Given the current life expectancy of persons and the increasing rates of malignant melanoma, it is estimated that 1 out of 200 Caucasians living in the U.S. in the year 2000 will have a melanoma.

However, as we have seen by the above data, melanomas are not the private domain of the Caucasian. All races are susceptible to melanomas, basal cell cancers and squamous cell carcinoma.

With early diagnosis and proper treatment, the diagnosis of melanoma need not be a death warrant. Hawaii physicians must be aware of the clinical characteristics of melanoma, basal cell and squamous cell cancers. They must help their patients become a part of the health team. Patients must be given brochures to teach them to look for the early signs of melanomas and skin cancers.

Brochures with excellent color photographs are readily available from the American Cancer Society, The Skin Cancer Foundation, The Skin Phototrauma Foundation and from members of the Hawaii Dermatological Society.

Patients must be taught that the regular daily use of sun protectives with an SPF of 15 or higher not only will reduce the aging effects of the sun in Hawaii, such as wrinkles and actinic keratoses, but will reduce the chances of getting skin cancer and melanoma. Children who are taught to brush their teeth on a regular basis should also be taught to put on sunscreen every morning.

Avoidance of noontime outdoor activities is a must for residents and visitors alike. There are dozens of activities that can be enjoyed indoors during the peak ultraviolet-ray exposure hours of 10 AM to 3 PM. Protective hats and lightweight garments now are readily available if patients must be out in the open at "high noon."

We should not scare our residents and tourists away from the beaches and the great outdoor activities in Hawaii, but we must educate them to enjoy these activities—in moderation and with common sense.

We must "Practice Safe Sun—Hawaii."

ACKNOWLEDGEMENTS

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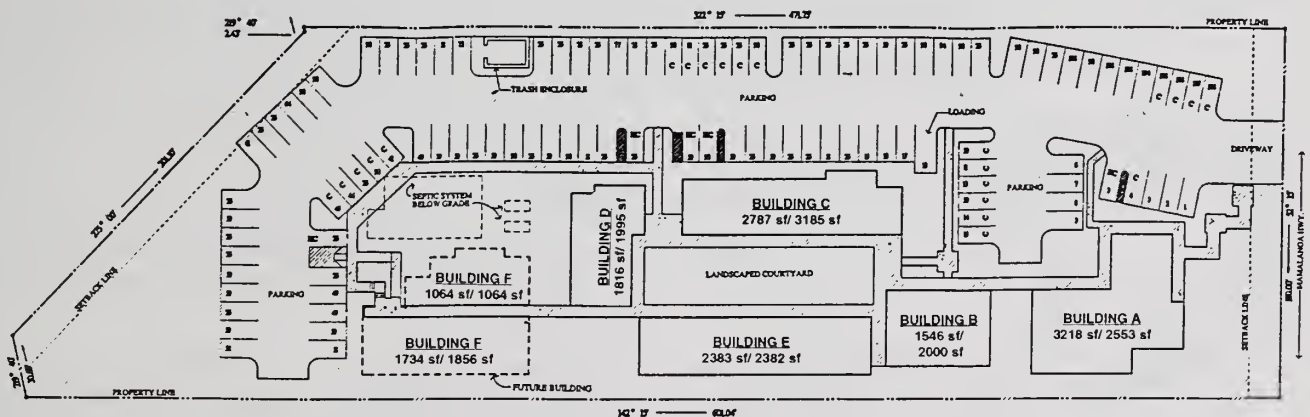
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Surgical Treatment of Melanoma

Scott Hundahl MD, FACS, FSSO*

"Malignant melanoma writes its message in the skin with its own ink ... some see, but do not comprehend."¹ Effective treatment of melanoma begins with early recognition. Paranoid suspicion of any irregular, pigmented, nodular or ulcerated dermal lesion, when coupled with excisional biopsy, merits approbation even though many such lesions prove benign.

Biopsy

In addressing controversial aspects of biopsy, infiltration of tissue with local anesthetic around a melanoma jeopardizes neither local control nor survival². Similarly, a delay of treatment for as much as 4 weeks following even incisional biopsy fails to alter local control or prognosis. Shave biopsies of melanomas should be avoided, as this technique interferes with accurate depth assessment and makes appropriate treatment selection nearly impossible.

Primary excision

Historical recommendations concerning margins of excisions in the treatment of primary melanoma seem largely a function of surgical tradition rather than science. In collected, retrospective series, local recurrence following primary surgical treatment approximates 3%³. Presence of risk factors such as ulceration of the primary tumor thickness > 4 mm, or location in the hand, foot or scalp has been reported as increasing local recurrence rates to 10% or more. A prospective study of 612 patients with non-ulcerated extremity melanoma < 2mm in depth, randomized to 1 cm versus 3 cm excision margins, failed to detect any significant difference in local control or survival. All 4 patients with local recurrence in this study underwent excision with 1 cm margins, however, and all had melanomas thicker than 1 mm; 2 of the 4 died of disease⁴. Thus, while 1 cm margins seem fine for < 1 mm thick melanomas, thicker lesions may warrant wider excision. An ongoing, prospective, randomized intergroup trial, in patients with non-ulcerated melanomas 1 mm to 4 mm thick, comparing primary excision with 2 cm margins versus 4 cm margins, should clarify this issue.

Tradition dictates primary excision of melanomas en bloc with the underlying superficial muscular fascia. Olsen's view that resection of fascia might allow dissemination from subdermal lymphatics⁵ prompted some to abandon this tradition. In a retrospective, non-randomized comparison, both local recurrence and survival in 107 patients with melanoma excised en bloc including underlying fascia, closely matched that in 95 patients whose underlying fascia was left undisturbed. Fascial excision can probably be done safely only in those with thicker melanomas.

Therapeutic treatment of involved lymph nodes

In a group of 1,134 patients undergoing therapeutic lymphadenectomy for pathologically involved regional lymph nodes, Morton and colleagues report 5-, 10-, and 15-year survival rates of 46%, 41%, and 38% respectively. Multivariate analysis of this large group demonstrates that an increasing number of involved nodes, greater Breslow thickness of the primary, and torso, head or neck location all independently decrease survival. Male gender and degree of involved nodal enlargement impact the result adversely with borderline statistical significance⁶. Patients with only 1 positive node enjoy 5-year survival of 79%¹⁰. Contrary to prevailing opinions that patients with involved nodes inevitably harbor occult distant metastases, results indicate a surprising proportion can be cured by means of a radical regional procedure. Radical lymphadenectomy remains the mainstay of treatment in such patients.

Some patients present with regional lymph node involvement without a detectable primary lesion. Overall survival of these patients following regional lymphadenectomy approximates that in patients in whom one can identify a primary¹¹.

Elective lymphadenectomy

After 2 prospective, randomized trials of elective lymphadenectomy versus observation (with therapeutic lymphadenectomy if indicated) failed to reveal any significant difference in 10-year survival, most surgeons abandoned unselective, routine, elective lymphadenectomy in melanoma patients¹²⁻¹⁴. Balch, analyzing biologic risk of both nodal and distant metastases according to thickness of the primary lesion, emphasizes that, while benefit seems unlikely in both those with relatively thin melanomas, ie low risk of lymph node involvement, and in those with advanced, thick melanomas >4mm deep, ie high risk of systemic spread—the so-called "intermediate subgroup"—at high risk for occult nodal disease but at lower risk for occult systemic metastases, might indeed benefit from elective lymphadenectomy¹⁵. Analyzing data from both large retrospective, and prospective, randomized lymphadenectomy series, Balch identified apparent survival advantage in this variably defined "intermediate subgroup"¹³.

To further evaluate elective lymphadenectomy in this subgroup, patients were added to an ongoing intergroup trial of 1-mm to 4 mm-thick melanomas, underwent secondary randomization: Elective lymphadenectomy versus observation. Results of this trial should finally lay to rest any residual controversy concerning elective lymphadenectomy.

An alternate approach to elective nodal surgery in melanoma patients with nonpalpable nodes, pioneered by Morton and colleagues, involved selecting patients for lymphadenectomy based on results of dye-directed biopsy of sentinel nodes; if such sentinel nodes harbor microscopic disease, lymphadenectomy is performed¹⁶. Given the reality of "skip"

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(Continued on page 132) ►

**OZONE DEPLETION: CAUSES,
POTENTIAL EFFECTS, AND
REMEDIES** (continued from page 122)

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metastases in melanoma, and the threshold of resolution inherent in even the best pathologist's microscopic analysis, having a "negative" sentinel node may not guarantee freedom from eventual nodal involvement. This intriguing approach certainly merits further study, however.

Locally advanced melanoma and in-transit metastases

Major amputation in patients with recurrent, locally advanced, or in-transit melanoma—usually performed in the setting of extensive, necrotic, bleeding or fungating lesions with or without in-transit metastases—generates long-term, disease-free survival in 20% to 49% of patients, again indicating that even extensive local-regional disease does not inevitably presage systemic involvement¹⁷.

Hyperthermic, isolated extremity perfusion combined with chemotherapy and lymph node dissection (and often surgical excision of gross disease) generates long-term survival similar to amputation¹⁷⁻²⁰. Today most surgeons preferentially treat patients presenting with locally advanced disease and in-transit metastases in this manner.

Adjuvant hyperthermic limb perfusion and elective lymphadenectomy

Encouraged by the apparent ability of hyperthermic, isolated-limb perfusion to control locally advanced and in-transit disease, Ghussen and colleagues at the University of Cologne conducted a prospective, randomized trial of this versus elective node dissection alone. At almost 6 years median follow-up, they report 90% 5-year actuarial survival in the perfused group versus 62% in the group not perfused ($p < 0.01$)²¹. In contrast to others¹⁸⁻²⁰, they report no limb-loss complications from the treatment. Results of this treatment remain unsurpassed by other adjuvant treatment schemes, but have not yet been independently confirmed or reproduced by others.

Surgical resection of isolated metastatic disease

Overett and Shiu, reporting results of a retrospective study of 176 patients undergoing surgical resection of distant metastatic deposits of melanoma, found that 33% of such patients undergoing complete resection of single-site disease survived 5 years. In contrast, those undergoing incomplete resection suffered prolonged hospitalization, considerable morbidity and negligible benefit, this emphasizes the importance of mature surgical judgment and judicious selection of patients when considering such an approach²².


Summary

Surgical resection of disease constitutes the mainstay in primary treatment of localized and regional melanoma, offering long-term survival far in excess of any competing treatment to date. Some highly selected patients can even benefit from surgical treatment of isolated distant disease if complete resection can be achieved. Adjuvant treatments performed in conjunction with surgical procedures such as isolated hyperthermic limb perfusion continue to hold promise for improving survival.

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Mohs Micrographic Surgery: A Synopsis

Jenny L Stone MD*

Mohs micrographic surgery is a method for removal of non-melanoma skin cancer in thin layers, allowing frozen-section examination of all peripheral and deep margins. Subsequent tissue layers are removed as dictated by microscopic examination, allowing for maximal sparing of normal tissue. This method offers cure rates significantly higher than excision or other modalities. Mohs micrographic surgery is the method of choice for removal of large, recurrent or incompletely excised skin cancers or for tumors located in regions of high recurrence.

Nationally, it is estimated that more than 500,000 new cases of non-melanoma skin cancer (primarily basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)) are diagnosed each year¹. With exposure to the sun being the most important risk factor, Hawaii can be expected to have a high incidence rate. Indeed, skin cancer rates on Kauai, observed prospectively for 5 years, appear disproportionately high to the rest of the nation in unpublished data.

The majority of these cancers may be effectively treated with as compared curettage and electrodesiccation, excision, cryosurgery and irradiation. However, certain subsets of these carry with them higher recurrence rates and present a more demanding therapeutic challenge. Mohs micrographic surgery has emerged as the most reliable and effective method for removing the more difficult non-melanoma skin cancers. Mohs surgery offers maximal normal tissue preservation as well as the lowest recurrence rates of all current modalities for the treatment of non-melanoma skin cancer at high risk for recurrence.

Historical background

Frederic Mohs developed the technique originally in the 1930s at the University of Wisconsin. He applied a fixative paste of zinc chloride and stibnite directly to a patient's skin cancer, the paste was allowed to fix the skin overnight, and then the fixed skin was removed (without bleeding or need for local anesthesia) the following day. The tissue was processed using horizontal permanent sections after carefully mapping, grossing and color-coding the tissue to maintain strict orientation. The tissue was examined by Mohs for remaining tumor, which, when found, was drawn on the map as a positive area. The process was then repeated daily, removing tissue only in the remaining positive areas until the patient was tumor-free. This technique, called chemosurgery, was published in 1941² and was found in this and in subsequent studies to result in extraordinarily low recurrence rates, in the range of 1% or

lower for primary BCC^{2,3,4,5} and 2% to 4% for recurrent BCC^{2,6,7,8}.

In light of the extraordinarily low recurrence rates as a result of chemosurgery, some investigators began to modify the technique. Tromovitch and Stegman of the University of California at San Francisco found that fresh tissue, rather than fixed, removed from the patient and processed as frozen sections yielded equally good results as the fixed technique^{9,10,11}. In addition, the fresh tissue modification offered 3 advantages: 1) the pain from in situ tissue fixation was avoided¹; 2) multiple stages (layers of tissue removal) could be performed in one day, shortening considerably the time needed; and 3) the post-fixation tissue slough was avoided, allowing for immediate reconstruction.

Because of these distinct advantages, the fresh tissue technique has virtually replaced the fixed technique. The term "chemosurgery" is of historic value at present. With universal acceptance of the fresh tissue modification, the technique was renamed "Mohs micrographic surgery" in 1981^{13,14}, by the American College of Micrographic Surgery and Cutaneous Oncology.

Indications

Mohs surgery is an ideal method for precisely removing non-melanoma skin cancers that are more likely to recur, and those whose clinical margins are unclear or inaccurate. In general, there are 5 main predictors of skin cancers that will have a higher recurrence rate: 1) An aggressive histologic subtype; 2) regions of the human body with a higher recurrence

TABLE 1

Aggressive Histologic Subtypes

Morpheaform or fibrosing BCC
Adenoid BCC
Infiltrative BCC
Micronodular BCC
Metatypical BCC (Basosquamous CA)
Anaplastic SCC
Acantholytic SCC
Dermatofibroma sarcoma protuberans
Microcystic adnexal CA

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rate; 3) recurrent tumors; 4) clinical size > 2 cm; and 5) incompletely excised tumors.

Aggressive histology refers to several subtypes of non-melanoma skin cancer that routinely have microscopic extensions beyond clinically apparent margins. The most commonly encountered aggressive subtypes for which Mohs micrographic surgery is appropriate therapy are listed in Table 1. Subclinical extensions of morpheaform BCC in one study¹⁵ averaged 7.2 mm beyond clinically apparent margins. Figure 1 shows a preoperative clinical



Figure 1: Preoperative appearance of morpheaform BCC

appearance of a patient with morpheaform BCC. The postoperative appearance, after Mohs sections were shown to be tumor-free, is shown in Figure 2.

Location of a non-melanoma skin cancer is somewhat predictive of likelihood of recurrence. Certain locations of BCC of the head and neck result in higher-than-expected recurrence rates. These locations are depicted in Figure 3¹⁶ and include the nose (especially tip, ala, dorsum), nasolabial fold, columella, philtrum, periorbital areas, pre- and postauricular areas, temple, and the helix of the ear^{17,18}. SCC recurs more frequently and is more likely to metastasize when located on the ear, lip or in a burn scar¹⁹. In addition to the higher recurrence rate of central facial and periauricular lesions, these areas also command a great deal of functional and/or cosmetic importance. Maximal sparing of normal tissue, as well as high

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cure rates may be best achieved with Mohs surgery in these areas.

Recurrent non-melanoma skin cancers pose a challenge to any modality of treatment. Recurrent tumors may track along old scar tissue and thus grow in an irregular fashion, producing subclinical extensions. Mohs surgery affords the highest cure rate compared with any other modality for recurrent BCC and SCC^{19,20} and is the treatment of choice for recurrent lesions.

Tumor size (preoperative) of > 2 cm carries an increased recurrence rate due to greater subclinical extensions²¹. In addition, SCC > 2 cm also has an increased metastatic potential¹⁹. Mohs reported a cure rate of 99.8% for BCC < 2 cm³. This rate decreased to 98.6% in tumors > 2 cm. By comparison, a study from NYU¹⁸ calculated the overall 5-year cure rate in primary BCC treated with excision to be 90.7%. The cure rate dropped to 87.9% in tumors >1.5 cm and 76.9% in tumors > 3 cm.

Incompletely excised tumors (recent excision with positive margins histologically) pose a high risk of recurrence if no further therapy is given. Pascal²² found that BCC treated by excision and found to have tumor present within 1 high-power field of the surgical margin showed a 12% recurrence rate if merely observed clinically. This rate increased to 35% when

the tumor actually involved the surgical margin. Positive margins indicate an extension of tumor that was not otherwise apparent clinically. The most definitive method of ensuring that the margins are clear is subsequent treatment by Mohs.

There are several other situations in which Mohs is favored as a method of treatment. A BCC or SCC with perineural spread carries an increased risk of recurrence. BCC in a patient with basal cell nevus syndrome may be aggressive, making tissue-sparing especially important; such cancers also are more numerous. Some less common skin malignancies also are amenable to Mohs surgery, such as verrucous carcinoma, sebaceous carcinoma, eccrine carcinoma (especially microcystic adnexal carcinoma), and dermatofibroma sarcoma protuberans. Some Mohs surgeons have applied this method of removal to melanoma; however, its use in pigmented lesions is not universally accepted and remains controversial.

Preparation

A patient referred for Mohs surgery should have had a prior biopsy with report and have slides available for review by the Mohs surgeon. A preoperative visit is ideal as the patient's medical history can be reviewed and any special requirements on the part of the patient (such as discontinuing anticoagulants, arranging for anticipated repair with a reconstructive surgeon, initiation of any prophylactic antibiotics) can be planned. The

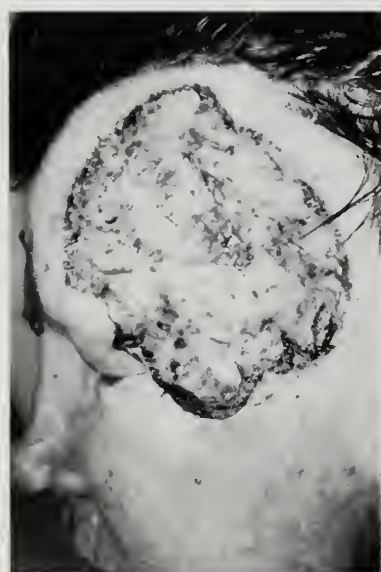


Figure 2:
Postoperative
appearance
of patient in
Figure 1

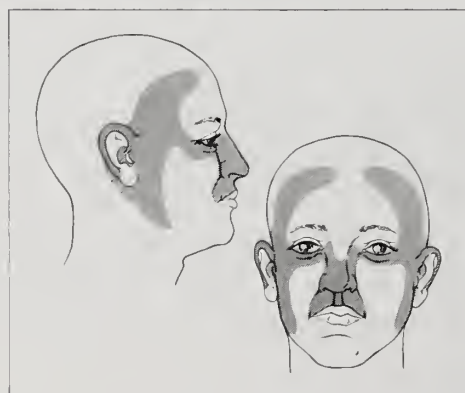


Figure 3:
Areas with
high risk of
BCC
recurrence*

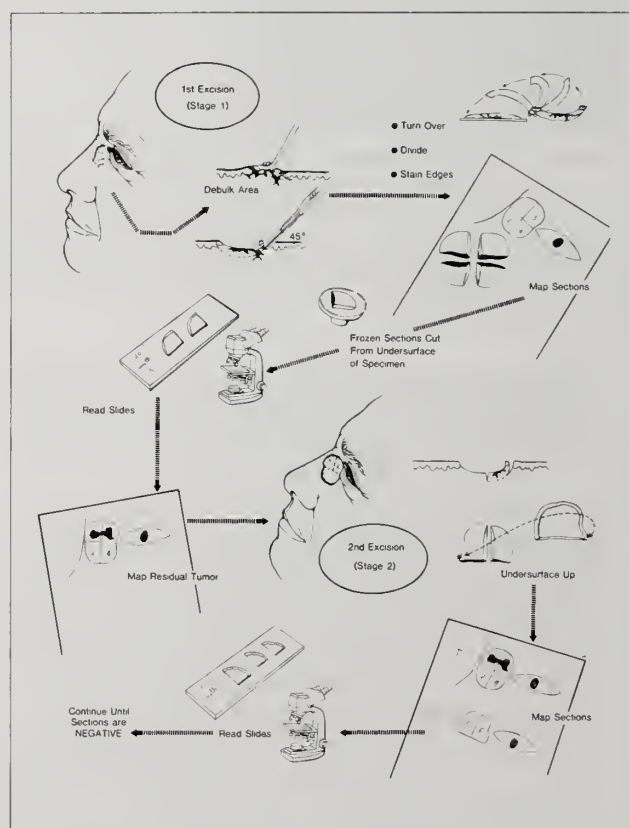


Figure 4: Schematic of Mohs micrographic surgical technique*

lesion size may be determined on an initial visit and, if it is large, the case can be scheduled appropriately. Lesion size on clinical inspection, however, is not always accurately predictive of actual microscopic extent of tumor.

Technique

The procedure usually is performed in an outpatient setting, generally in a clinic, using local anesthesia. The tumor is first debulked, removing obvious cancer cells with a curette or scalpel. This process is outlined in Figure 4. A thin layer of tissue is then removed with a scalpel, beveling the edges to 45 degrees. Orientation is strictly maintained throughout the procedure. Several small cuts (scores) are made in the specimen and at the surgical site for alignment. Hemostasis is achieved with electrocoagulation and/or suture ligation, the patient is bandaged and is free to relax and wait in the waiting room while the tissue is being processed. The skin is mapped and divided into pieces of appropriate size by a technician (usually no larger than 1 cm) for frozen sectioning. Contrasting dye is used to mark cut edges to assist in orientation. The specimen is flattened on a glass slide to bring the epidermal edge into the same plane as the deep margin. The tissue is frozen in this position in a cryostat. The skin is then cut into horizontal sections on a cryostat, taking care to align the tissue chunk properly to ensure a complete section. Meticulous flattening of the tissue and positioning of the tissue chunk in the cryostat are essential in producing suitable horizontal sections. For this

reason, cryostat models that do not allow flexible positioning of the tissue chunk are not appropriate for this procedure. The frozen sections are then stained, coverslipped and presented to the Mohs surgeon for interpretation. The slides are examined by the surgeon for evidence of remaining tumor and areas noted to be positive for tumor are clearly marked on the tissue map.

The patient then returns to the treatment room for removal of additional tissue. By comparing the tissue map to the operative site, only tissue in the positive area will be removed, sparing tissue observed to be tumor-free. The process is repeated until all the sections are found to be negative. Of prime importance is the fact that the Mohs surgeon acts as both the surgeon and the pathologist. The orientation of the specimen in this procedure can be lost or obscured when more than one person performs both roles.

Unlike routine pathologic examination of excisions, the entire peripheral and deep margins are examined in Mohs sections. Traditional histologic exams of excisions, even wide excisions, only sample the margins in several areas. Statements of "margins free of tumor" on pathology reports do not imply that all of the margins were examined.

In cases of aggressive spread of tumor into vital structures such as ear canals, orbits, bone, major nerve trunks, it may be necessary to work in conjunction with physicians from other specialties. In such cases, an ENT surgeon, for example, may be guided by the Mohs surgeon to an area that remains positive for tumor in an ear canal or nasal bone. This may be done in an operating room setting under general or IV anesthesia.

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Sometimes it is necessary to process a tissue layer in permanent sections often necessitating a 1-day wait for results in cases where bone is involved (requiring decalcification) or in tumors found difficult to discern on frozen section.

Recurrence rates

A thorough review of the literature and a weighted comparison of recurrence rates from all modalities was done in 1 study for primary BCC²³. Looking at 5-year follow-up of primary BCC recurrence, surgical excision showed a 10.1% recurrence rate, curettage and electrodesiccation (C&E) a 7.7% recurrence, radiation therapy a rate of 8.7% and cryotherapy a rate of 7.5 %. Some caution is advised in considering rates in C&E and cryotherapy because large, high-risk lesions may not have been included in many of these studies.

Overall all non-Mohs modalities had a recurrence rate of 8.7%. At 5-years' follow-up, removal by Mohs surgery resulted in a recurrence rate of 1%.

A similar study on recurrent BCC²⁰ with 5- year follow-up also was observed. Surgical excision showed a recurrence rate of 17.4%, radiation therapy a rate of 9.8% and C&E a rate of 40%. Cryotherapy had a short-term recurrence rate of 13%, but there was no data on cryotherapy 5-year follow-up.

All non-Mohs modalities had an overall recurrence rate of 19.9%. Mohs surgery showed a weighted average of 5.6% recurrence rate 5-years later. Therefore, according to these studies, non-Mohs modalities have a recurrence rate 8 times that of Mohs in primary BCC and 4 times that of Mohs in recurrent BCC.

In primary SCC of the skin, a similar study examined the 5-year recurrence rate using the following therapeutic methods¹⁹: Surgical excision had a local recurrence rate of 8.1%, curettage and electrodesiccation a rate of 3.7, and radiation therapy a rate of 10%. Again, there may have been some bias in selection with respect to the C&E modality, as this method is not used very often in large, high-risk SCC. Overall non-Mohs methods show a 5-year recurrence rate of 7.9%.

Mohs surgery was found to have a 3.1% recurrence rate after 5 years. In locally recurrent SCC, surgical excision had a 5-year recurrence rate of 23%, compared with a 10% recurrence rate with Mohs surgery.

Several factors increase risk of recurrence or metastasis in SCC, including the degree of differentiation, the size of the tumor, its depth and site. In SCC of ≤ 2 cm, surgical excision affords a cure rate of 83.5%, but when > 2 cm, the cure rate drops to 58.3%. Comparison with Mohs shows 98.1% and 74.8% cure rates respectively. Surgical excision of well-differentiated SCC offers a cure rate of 81.0%, but this drops to 46.4% for poorly differentiated SCC. By comparison, Mohs cure rates are 97% and 67.4%, respectively. Mohs surgery affords the patient with SCC a significantly increased cure rate, even in cases at high risk for local recurrence and metastasis. Lower cure rates for Mohs surgery in poorly differentiated SCC may reflect the tumor's propensity for early metastasis; it is also more difficult to define this tumor on frozen section.

The pros and cons

As described above, Mohs micrographic surgery offers significantly increased cure rates in cases of BCC and SCC as compared with other methods. In addition, maximum sparing of healthy tissue is achieved; this is of prime importance when cancers occur on the face and ears. The vast majority of Mohs surgical procedures are done using local anesthesia in an outpatient setting, avoiding the risk of general anesthesia and operating room charges. Long-term cost is less, as recurrence is much less likely, thus avoiding subsequent procedures.

A relative disadvantage is that special training is necessary to perform Mohs micrographic surgery. Typically, fellowship programs require 1 to 2 years' training after a dermatology residency (or after an ENT or plastic surgery residency). A laboratory setting that incorporates a cryostat and staining hood also is necessary. It is essential that an expert technician be available who has had special training in preparing Mohs sections.

Mohs surgery is certainly more time consuming than other modalities, the time spent in processing often runs from a half hour to 1 hour per stage. Very large tumors may require numerous sections and will take several hours to process. This fact may deter some patients who may be unable or unwilling to wait for the tissue to be processed. The short-term costs of the procedure also are greater than those of other previously mentioned methods.

Conclusion

Mohs micrographic surgery offers the highest cure rates at present for non-melanoma skin cancer. It is the method of choice for patients at high risk of recurrence of non-melanoma skin cancer: Those with large, recurrent, incompletely excised or aggressive tumors or with tumors in areas of high potential for recurrence. Practitioners who evaluate patients with non-melanoma skin cancer are well-advised to be familiar with this method in order to give proper informed consent to their patients about the choice of therapeutic methods.

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The Kauai Skin Cancer Study—1983 to 1992

George T Reizner MD*

The Kauai Skin Cancer Study began as a modest effort in 1983 to look at this island's skin cancer incidence. David Elpern MD, Kauai's only dermatologist at the time, was interested in the large number of these tumors in his practice. He first enlisted his office staff to help keep track of the numbers and type of these skin cancers. Along with this information, the basic demographic data on each patient was collected. These records became the first entries into what has become a decade-long project.

Hawaii's strong ultraviolet light and predictable good weather create an opportunity to study solar radiation's effect on a population. This, coupled with the outdoor life-style of many of its residents and visitors theoretically increases the risk for skin cancer.

The collection of data on Kauai was simplified by several features, making this island a good site for study. There is only one pathology laboratory, which greatly standardizes data and case identification. Also important, most patients seek their medical care on island; therefore, with good confidence, most biopsy-proven cases can be captured. Even if another physician treated the patient on Kauai, the pathology specimen would pass through the one laboratory allowing it to be included in the count.

The presence of several different ethnic groups on Kauai invites the simultaneous study of these different types in the same environment. This one feature alone led to several publications reporting the lesser-known incidence of skin cancer in non-Caucasian populations. All of these preexisting conditions and circumstances allow for easier collection of data and underscore this setting's value as a site for investigation.

The Kauai skin cancer study includes not only basal cell carcinomas and squamous cell carcinomas but also records the incidence of Bowen's disease, keratoacanthomas, melanomas, and various other uncommon cutaneous malignancies. This expanded list enables us to check more reliably their frequency, especially when recorded over many years.

Now, 10 years later, the scope of the Kauai Skin Cancer Study has exceeded its original design. Kauai, as a natural laboratory, has shown itself well suited to the study of skin cancer with several papers already published that discuss the results and experience of this project.

One of the first articles examined the relative increase in non-melanoma skin cancers in the Kauai Japanese population as compared to the experience in Japan¹. The crude rate of

skin cancer found in Kauai's Japanese patients was 88 times greater than that reported in Japan. Interestingly, the tumors here occurred only in patients >60 years old. When the age-adjusted rates were calculated with this in mind, an incidence 33 times greater than in Japan was reported.

Although the absolute rates were still much lower than those reported in the Caucasian population, this unexpected finding in the Japanese contained several messages. First, as originally suspected, the incidence of skin cancer on Kauai was proving to be an increased health risk. Second, both the lower incidence when compared to Caucasians plus the relatively delayed tumor onset in this non-Caucasian population reinforced the concept that partial but incomplete protection from tumor formation was conferred by darker skin. Third, it showed monitoring several ethnic groups in parallel was proving valuable; and finally, that probably all these groups were at some increased risk.

In an article recently accepted for publication, we looked at the skin cancer incidence in our Caucasian population. Kauai has the dubious distinction of having the highest reported rate of basal cell carcinomas currently observed in the United States. Work in progress based on this data includes studies documenting the incidence of basal cell carcinoma on Kauai and particularly of keratoacanthomas. A third investigation looks at the incidence of basal cell carcinomas, squamous cell carcinomas and keratoacanthomas in the Filipino population, and a fourth will report on basal cell carcinomas and keratoacanthomas in Hawaiians. Papers on these topics have already been accepted by peer-reviewed journals.

An important work underway is our 10-year experience with malignant melanoma. Many useful insights may be possible by cross-referencing these patients with those in the non-melanoma study. It is still too early to speculate, yet certain skin cancers or combinations of skin cancers may serve to alert us to a higher risk of melanoma. The outcome of this part of the project is being awaited with heightened interest.

The future for the Kauai Skin Cancer Study is equally interesting as we pursue many additional venues of investigation. This data base, which is currently supported by a Veterans Administration Merit Grant, has shown itself to be a rich source of information. The final years of the 10-year study are being collected and prepared for statistical analysis.

The study has been a cooperative effort by many physicians and scientists. Dr. Evan Farmer from Johns Hopkins read many of the early slides; Tsu Yi Chuang MD MPH from Wright State University has added his epidemiological skills and been instrumental in writing papers and grants. Jenny Stone MD from the Straub Clinic & Hospital in Honolulu has seen and treated patients, collected information from them

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and has done much of the early computer work. The entire dermatologic staff at the Kauai Medical Group deserves both praise and thanks. Additional special recognition goes to Terrilea Burnett, whose thoroughness contributed significantly to each phase of this project, and Katie Beer, who has assumed many of the same responsibilities.

The team of pathologists at GN Wilcox Memorial Hospital in Lihue: Rex Couch, Gerald Tomory, Jonathan Charles, and posthumously Robert Emrick, plus their office personnel, Louise Yates and Fern Bungcayao, have been indispensable in offering learned opinions and in collecting and retrieving thousands of cases. Without their support, interest and help, we never could have undertaken this study. I have served as a liaison to help hold the project together. Over the years I have logged many long hours of reading slides, contacting patients, entering data, combing through charts, writing papers and attending to many extra details. My reward has been the satisfaction of seeing this project through and the opportunity to travel from the Mainland and visit this beautiful island regularly.

Finally, although many have collaborated at various levels for the success of this project, it is David Elpern's initial interest that made it possible. Those of us involved are grateful for his continuing contribution and salute his curiosity that enabled him to conceive and shape this program.

Summary

The Kauai Skin Cancer Study offers a small glimpse into understanding cutaneous malignancies. Through these efforts valuable data may be gathered. It is hoped this can be translated into useful clinical information with a positive impact on both public health education and medical care.

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Learning to Save Our Skin

Paul Berry*

With serious depletion occurring in the stratospheric ozone layer, we face a public health problem that poses an educational challenge as well. How do we teach our children about the hazard and how to respond to it? Although we have the science to demonstrate the problem, changing young people's behavior on a large scale is at best a slow and uncertain process, especially when the behavior involves something most of them perceive as a familiar pleasure and a reward: The Hawaii sun.

The task of teaching others about ozone-depletion and the health hazards of ultraviolet rays was posed to students (grades 10 through 12) in my Earth-at-Risk class at Punahou Academy, and we have spent 9 weeks learning about the problem and developing a variety of ways to educate others about the need to use sunscreen. It is a curious undertaking, for it involves students collaborating with dermatologist Dr. Norman Goldstein, the Sea Grant Program at University of Hawaii, the Cancer Society, the Department of Health, a representative from the Department of Education, and finally teachers throughout our school. In short, this is a different model of education, one aimed at providing others a service that they may not realize they need. The basic premise lies in the assumption that, armed with the right information and a variety of approaches, children may be more credible as public health teachers than adults or authority figures.

As they have learned about ozone depletion, the increase in UV rays and consequent health risks, students have examined their own attitudes in hopes of understanding how other young people might resist what they need to learn. Here are some of the assumptions they have used in developing approaches to teaching others about increased hazards of sun exposure.

1. Once you know the extent of ozone depletion and the increase in UV rays, you have a clear responsibility to teach others. Kids, however, are not always willing to take responsibilities.

2. If you tell people that there is an invisible layer of something overhead that has a hole in it, listeners at first feel puzzled. If you say there is a new hazard in sunlight from rays you can't see, you run a similar risk.

3. Students who don't feel strong in science may tune-out when asked to examine the chemistry of ozone depletion.

4. When the discussion suggests this ozone depletion means that time spent in the sun needs to be altered, the listener's defenses rise and denial is quite normal.

5. While denial is quite powerful, the combination of peer pressure, a positive approach, and testimonials from other young people whom kids admire can move young people of all ages onto the sunscreen bandwagon.

6. The information has to appear in a variety of forms, not all of them academic; TV is a must.

7. Young people are naturally concerned about their appearances and a tan is presently perceived as attractive. Our sunscreen program is working against a youth-culture tradition. On the other hand, a poster showing facial wrinkles caused by exposure to the sun sets off strong reactions among teenagers. Teenage women who are concerned about makeup being disrupted by sunscreen will be more concerned about what wrinkles can do to their appearance.

8. Kids naturally feel immortal and focus on the moment or the near horizon. Talk of cumulative damage to skin, eyes or the immune system will have more impact if it comes from someone they know and trust.

9. We don't know what will get the best results in moving kids to the use of sunscreen, it may vary from student to student.

Because all curricula at Punahou are created by our teachers, we also agreed that the real job lay in getting the full attention of teachers, ie to have them take what we would give or point out to them and find ways to tailor units for their own classes.

After teaching high school for more than a generation, I believe that, regardless of the subject, kids face 2 questions in every class: What is going on here? and, what has it got to do with me? If they feel there is a significant answer available for the second question, they have a lot easier time becoming interested in the first question. In the case of the sunscreen issue, there is also an obvious third question: What can I do to protect myself?

My class discussed possible names for our program and settled on Save Our Skin; the acronym SOS was appealing and looked like a good prospect for an attractive logo. Next, we clarified what we were trying to accomplish. Students of all ages need to learn that: 1. A new danger exists in overexposure to the sun; 2. you may find the environmental causes of the hazard interesting because they are in part man-made, but you need to know the health consequences; 3. you can easily learn how to protect yourself, but it takes a change in attitude about time in the sun.

We are developing a package of materials for all teachers, kindergarten through grade 12. Before disseminating the information widely, however, we need to try the package on a few teachers first to see how useful it is. As we develop our materials, our initial push in elementary school will be through our outdoor education programs in grades 4, 6, and 8; all students in the grade spend anywhere from 3 days to 6 days in nature outdoors and have immediate need for sunscreen information. We also will provide packages to physical education teachers at all levels, and to coaches of outdoor sports, along with sunscreen samples.

We hope to approach high school students through a variety of venues including posters, assemblies with slides and testimonials, and classroom teaching units.

Our goal is to motivate all 3,700 Punahou students to put on sunscreen (SPF 15 at a minimum) after a morning shower or in their homeroom meetings at the beginning of the school

* Teacher at Punahou School

day. To see how effective this program will be in our high school, we have selected 8 homeroom classes, 2 each in grades 9 through 12, to receive posters, information, and sunscreen. We will ask parents of these students to provide them sunscreen to bring to and use at school. If students do not bring sunscreen, we will ask parents for written permission for the school to provide an SPF 15 sunscreen, and we will encourage youngsters to use it. Funding for the sunscreen that Punahou provides will come through income from the school's recycling program with the City and County of Honolulu. After we track the use of sunscreen by students in these classes, we will revise our approach as needed to reach all 1,600 students in our high school.

In April this year we kicked off our program by putting up a variety of American Cancer Society posters in prominent places—in the cafeteria, at the entries to our libraries, and near club bulletin boards. Next, in an assembly, our senior students saw and heard a student slide show about safe beach-going and outdoor athletics, followed by brief remarks by student speakers—athletes, surfers, and class-leaders supplying sunscreen testimonials. Modified for each audience, students presented this same assembly to students in grades 9, 10, and 11.

Our teacher package will include an adaptation of the sunscreen booklet written and produced by Bruce Miller and Scott Bogle at the University of Hawaii Sea Grant Program. Additional copies of useful science and social studies lessons, along with news and scientific articles will be appended to the newly illustrated, 2-color booklet.

The causes and chemistry of ozone depletion offer a great opportunity for students to investigate a real-life environmental problem that affects them directly. Because the information shows UV conditions worldwide and has copies of NASA satellite photos, we hope that teachers will take advantage of the opportunity to teach geography, investigative science, politics, economics, and ethics: for here is an issue that has brought nations together in search of a way to halt man-made causes of ozone depletion. We also will include an art assignment to allow youngsters to depict their understanding of the problem and arrange to display their work in our libraries.

Miller and Bogle of Sea Grant have also shown students how to read UVB

(continued on page 144) ►

TAKING THE COMPLEXITY OUT OF INVESTMENTS

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FIGURE 1: Kanani Taliaferro and Suzie Oki trying a handheld UV ray meter

rays with a prototype hand-held Sunsor-meter that they have temporarily lent to us. When these meters become available commercially in the fall for about \$30, we plan to use some of the school's income from community recycling to buy a number of them for use in science classes from elementary through high school. By computer and modem, Sea Grant also has made available to us daily readouts of UV rays from the more sophisticated UV meters at UH Manoa and atop Mauna Kea on the island of Hawaii. Here is an opportunity for children to use technology to learn how to monitor shifts in stratospheric ozone and consequent increases in UVB rays, real science at the moment. Thus far, when students have measured the UV data themselves and have seen what it means in terms of their health, they are far more likely to become sunscreen-users.

With up-to-date UV measurements, people of different skin types can now establish how long a time they have in the sun before they will begin to burn. Local dermatologists have developed 4 categories of skin types: Always burns/ never tans; usually burns/sometimes tans; sometimes burns/ usually tans; never burns/always tans. Building on this information and on data from the producers of Sunsor-meter and from UH Sea Grant, my Earth-at-Risk students are now designing color posters to show what the UV readings mean for people with differing colors of skin. Students will be the models depicted on the posters as well as the photographers and graphic designers, collaborating with our media-support specialist. Once we have the prototype posters completed, we will be happy to share them with other agencies for their production and distribution.

Finally, because Punahou has video-production facilities and students taking advanced video production courses, 2 talented young video producers from our Television Journalism class have been assigned to work with 2 classmates from Earth-at-Risk to write and produce a 10-minute videotape in which kids teach kids about the need to use sunscreen. Like the slide show, the lighthearted, positive focus will remain on kids of various ages and skin colors involved in normal outdoor activities: Skateboarding, swimming, playing volleyball in the park, shooting baskets in the schoolyard, or just sitting in the sun.

Because video production is labor intensive, our students hope to complete their production and make it available for use at Punahou sometime in May of 1993. If the tape succeeds with its audience, we will make available a master to

private and public schools with which to make their own copies.

We are also examining other video productions which tell the story of ozone depletion and health hazards, and we hope to add a video bibliography of the best to our teacher package.

Because they are aware of the new potential for damage by the sun and hazards to health, Punahou President Rod McPhee and Principals Win Healy and Duane Yee have been very supportive of our efforts. By using students to teach other students, and by collaborating with Dr. Norman Goldstein, UH Sea Grant, the American Cancer Society and other community agencies, Punahou School hopes students will learn to save their skins for a lifetime.

Appendix

Save-our-skin materials

1. Questionnaire per age level concerning: knowledge of ozone problem, UV rays, sunburn frequency and impact, sun screen use.

2. Posters:

1. The hole story
2. Skin like leather
3. Ban the burn
4. Honolulu newspaper full-page copies
5. Student-made posters

3. Handout: Look for the danger signs; sample melanomas for ABCD.

4. Booklet for Teachers: ozone chemistry, causes; UV impact on all life; preventive measures against CFCs, etc; UV impact on human health, protective measures for human health. Reading. Sample quiz/questionnaire. Sample sunscreen experiment, with accompanying sunscreen samples.

5. Color slide/overhead projections of planet Earth receiving the sun's rays, and NASA satellite photos of ozone hole.

6. City by city, region by region UV-ray index.

7. Xeroxed news reports on the ozone hole and its consequences.

8. Xeroxed magazine and scientific articles.

9. Student-created poster with skin types. UV readings, and color pictures of skin types.

10. Student-created slide show on depletion of ozone, UV problems, causes, protections. Also has live teenage models (surfers, athletes, beach-goers) using hats and sunscreens.

11. Video productions: Student productions showing kids imparting message to other kids.

Commercials. Professional productions: Dick Cavett; preventive measures for CFCs etc.

Sunsor tape; After the Warming by James Burke

12. Permission slips for students to sign in order to use sunscreen.

13. Science and Social Studies curricular exercise Australian form.

14. Sample letters to write Congress, President, EPA, manufacturers.

15. Macintosh Computer game: Global Recall. Offers a simulated version of actual ozone data and possible solutions to examine.

16. Student art and student logos.

17. Sunsor meter available probably in fall for \$20 to \$30 to use in reading UVB rays. Useful to science labs.



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Editor's note:

Christine Trecker is a 20-year resident of Oahu. She lives on the windward coast with her husband and daughter and enjoys the indoors and outdoors. Her background is in marketing research and advertising.

She realized the need for this type of publication for our resi-

dents and our visitors as well. All profits from the book sales go to the Friends of Foster Kids. Books are available at Liberty House and most bookstores..

Norman Goldstein MD

NEW ULTRAVIOLET MONITORING (continued from page 116)

scientific and nontraditional settings. The EMTEC Uviscan™ PDU is a public display unit approximately 1 meter square (Figure 1). Data on UV intensity are displayed as individual "time-to-burn" values for each skin type. (The EMTEC Uviscan™ PDU has been calibrated for skin types 1 to 4.) The unit's display rotates through 360° to ensure maximum visibility from all surrounding areas. A measurement of UV is made at the beginning of a series of 4 rotations; the unit then displays the estimated time-to-burn for each skin type. When the cycle is complete, the UV sensor takes a new measurement and the display values for each skin type are updated. Measurements are made every 4 minutes, though this rate can be adjusted to suit the unit's particular application. The unit is intended for installation in public recreation areas such as beaches and playgrounds; Figure 1 illustrates the positioning of the EMTEC



Figure 1: Copyright EMTEC Ltd

Uviscan™ PDU above a lifeguard station on Waikiki Beach in Hawaii, one of the first sites to employ EMTEC technology. The unit has been designed so that the display is visible from up to 100 meters away, even under the most glaring conditions.

Two similar but smaller devices are presently being designed: The EMTEC Uviscan™ Professional and the EMTEC Uviscan™ Domestic. The Professional has been designed for use in commercial establishments with high popula-

tion density, where long-distance visibility is not essential. Hotel swimming pools and tennis courts are 2 typical applications for this device. The EMTEC Domestic has been designed for the home environment, again for use near the swimming pool or during children's backyard playtime.

EMTEC technology also makes possible accurate personal UV monitoring. The pocket-size EMTEC Uviscan™ Personal is an intelligent device that allows the user to insert his or her skin type, sunscreen SPF number and the amount of sun exposure per day. The Uviscan Personal then displays the estimated time-to-burn. Every 30 seconds the unit takes new measurements and updates the display accordingly.

A final product is designed for use on children. It is non-programmable, allows for only 1 skin type (type 1) and the parent is required to apply a sunscreen of SPF 15 or higher to the child. In this manner, EMTEC hopes to encourage a relationship between the regular use of sunscreen and an adequate SPF number for the child's protection against the sun. The unit measures and records accumulated UV exposure and displays the accumulated dose in the form of up to "10 suns" on a liquid crystal display. When the tenth sun has appeared, an alarm sounds which means that the child should be taken indoors in order to avoid overexposure.

Summary

The EMTEC sensors include a range of products appropriate for different uses in different locations. It is envisioned that this technology, used in conjunction with public health education, will have a significant impact on sun-oriented behavior. The message being delivered will be accompanied by quantified information directly useful for gauging sun exposure.

With the technological elements now in use, a low-cost, ground-based UV monitoring network can be established. EMTEC is actively establishing such a facility in association with interested organizations on a worldwide basis. Dissemination of this information will raise public awareness of skin cancer issues and assist institutions in vital research.

The development of the EMTEC sensor marks a new era in UV monitoring and places an emphasis on the responsible use of products based on new technology.

GENDER-RELATED ISSUES IN MALIGNANT MELANOMA (continued from page 124)

Centers for Disease Control (CDC) show that the death rate from melanoma in women increased 21% from 1973 to 1988 while the death rate for men increased 50%. In fact, according to the CDC, the death rate for melanoma in men is increasing faster than for any other cancer.

Conclusion

The incidence of melanoma is increasing most rapidly in women under 40 whereas the death rate from this tumor is rising more rapidly in older men. Because the only cure for this cancer remains early detection and treatment, increased public education and promotion of awareness among both women and men are needed in order to minimize the hazards from melanoma.

Editorial comment:

Dr. Rigel is a "world authority" on melanoma.

Norman Goldstein MD

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MAKA O KE KAUKA

Russell T Stodd MD

The trouble with the world is that the stupid are cocksure and the intelligent are full of doubt.

On March 29, 1993, the first open hearings on the Clinton health care plan were conducted by VP Albert Gore. Ms. Hillary Rodham Clinton was called away due to her father's illness. There was general praise for the plan from various interests, but also some heavy criticism. Specifically, representatives of the AMA, AHA, insurance groups, and research technology were united against wage and price controls. Ray Scalettar MD, chair of the AMA Board of Trustees, spoke clearly when he said that cost controls have never been achieved in this or any other economy by arbitrary caps on expenditures. Additional negative response came from business interests deploring the concept of employer-mandated health insurance. Washington rumors were that the hearings were largely for posturing and catharsis, and that the program has already been charted by HRC, her primary consultant, Ira Magaziner, and the 500-plus task force members.

They define themselves in terms of what they oppose.

In an effort to determine precisely who is on the Task Force for Health Care Reform, the *Wall Street Journal* obtained a list reluctantly supplied by the administration. Surprise! Bureaucrats—almost all are currently working in HCFA, HHS, other administration posts, and on Congressional staffs, plus a few academic wonks. Knowledgeable outsiders could find no (zero) representatives of organized medicine, managed health care, hospital associations, manufacturers of medical equipment and pharmaceuticals, not even any self-appointed consumer advocates (Sidney Wolfe/Ralph Nader). In fact, it is gratingly obvious that no one with true job experience in the field of medical care was invited to join the team. It might appear to some that our new administration has an attitude problem.

A patient will believe anything so long as it is not founded on medical science.

In treating our clientele, physicians labor under the assumption that patients are following a therapeutic program. However, studies have revealed that only 1/3 of patients use medications as prescribed, 1/3 use our prescription now and then, and 1/3 do not use medication at all. Furthermore, according to the *New England Journal of Medicine*, at least 1/3 of adults turn to alternative forms of therapy, e.g. acupuncture, biofeedback, massage therapy, chiropractic, aromatherapy, crystals and herbal compounds. On Maui, mother's milk remains a staple for treating the red eye. Of those patients who resort to alternative measures, fully 3/4 do not inform their medical doctor of such action.

Ninety percent give the other ten percent a bad name. The appropriate phrase is "Transfer of Wealth."

What it means is that income is shifted from the producers to the nonproducers. For the first time in American recorded history, in 1992 the number of employees working for federal, state and local governments surpassed the number of manufac-

turing jobs in the private sector. Military personnel are excluded. Supporting this government workforce requires the average family to pay \$16,110 in taxes each year. Hear the echo of the words from *Walden Pond*, "That government is best which governs least."

You can't say civilization isn't advancing.

They find new ways to kill you everyday. The fundamental Hippocratic approbation is "Do thou no harm." It would follow, therefore, that the ethical practice of medicine is concerned only with doing good, while respecting the personal rights and wishes of the individual patient. How shocking that 3 physicians were shot and wounded in the emergency room at LA County General Hospital by a disgruntled former patient. And in Pensacola, Florida, a physician, legally practicing medicine, was shot and killed by a self-appointed executioner. That such actions can occur might be explained as the vagaries of a demented mind, but the frightening aspect of the Florida episode was the callous statement of a few right-to-life(?) proponents that the executioner was justified!

The last time I voted was 1964; I voted for LBJ the peace candidate.

With the whittling down of the military, the need for health care personnel also has decreased. But what will the military do in the event of a national emergency? Medical care readiness has always been considered an "Achilles' heel" by the Pentagon, and legislation was proposed in 1986 requiring peacetime registration of physicians. Heavy lobbying by the AMA defeated that measure. Not to be undone, proponents of a draft bill slipped a version through Congress in 1987 allowing the Selective Service to develop a crisis plan. Therefore, a plan is now being devised to conscript health-care workers in the event of a national emergency, especially thousands of physicians under the age of 44. Targeted as the first to go would be young orthopedists, general surgeons and anesthesiologists, while the least likely would be internists, FPs, Ob-Gyns, and pediatricians. Of course, it is all on paper and would require the action of Congress and the President before becoming effective, but the Pentagon is thinking of you, and remember there are 5 sides to every Pentagon question.

Addenda

- ▲ Absurd recommendation on cataract guidelines, "Dilate the pupil to delay surgery!"
- ▲ Roman patricians overcame presbyopia by having their slaves read to them.
- ▲ If you happen to injure a groin muscle, be sure it isn't your own.

Aloha and keep the faith,

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Pregnancy and lactation: Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis, hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawal due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestolol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestolol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids (1 hour prior to PRAVACHOL), cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitals, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a $\geq 50\%$ rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retin-

nogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear (Wallerian-like) degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagenesis tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/– mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when the same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecostasia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol, and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

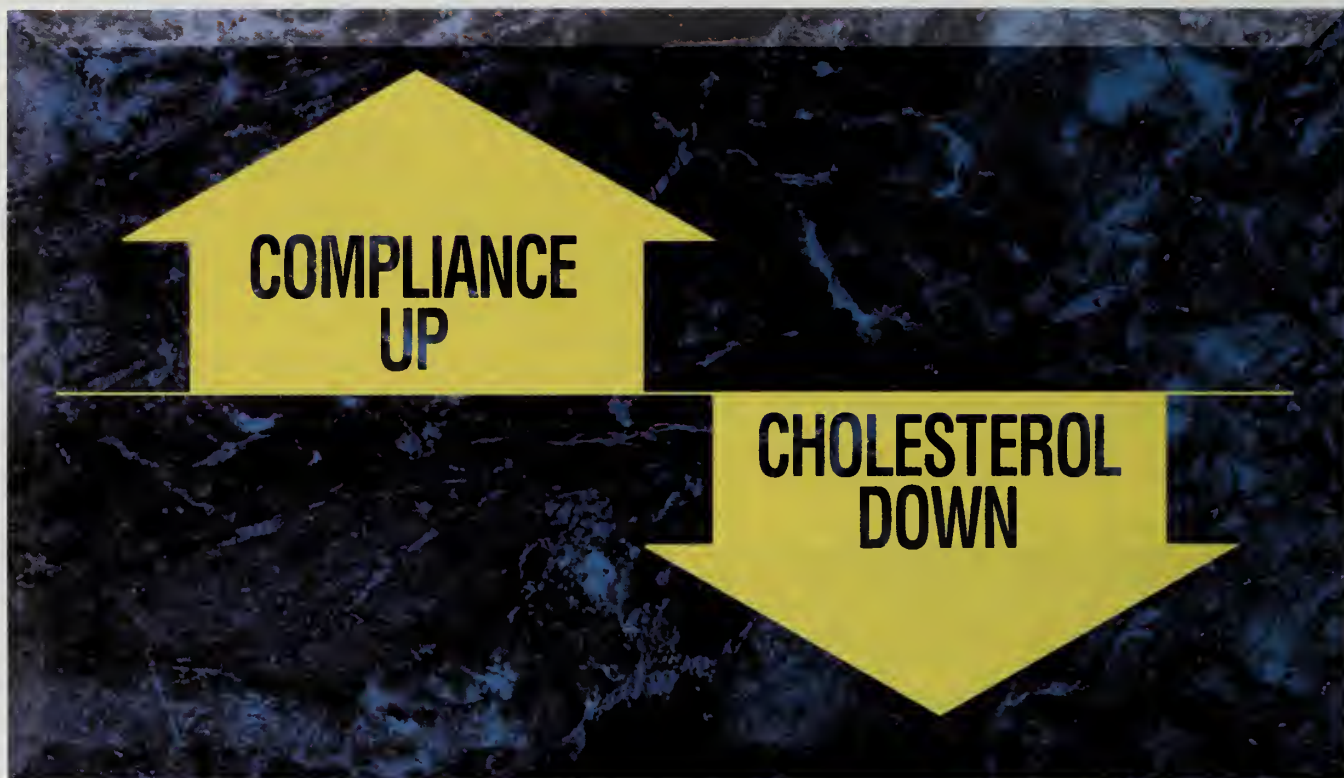
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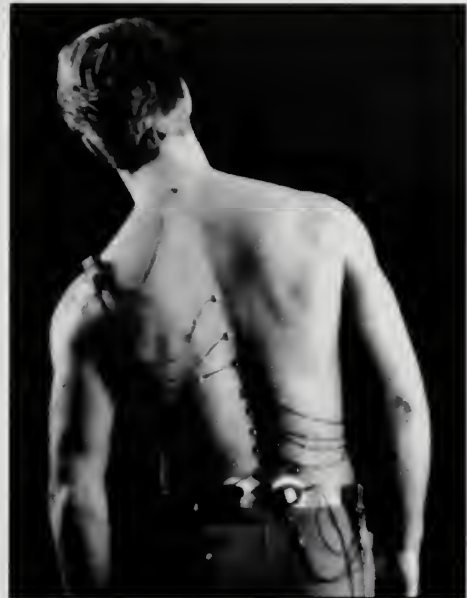
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Highlights of the HMA Council Meeting of April 2, 1993

Members present were: J Chang, A Don, J Spangler, F Holschuh, S Wallach, C Kam, R Stodd, C Lehman, B Shitamoto, R Goodale, H K W Chinn, W Dang Jr, P Hellreich, R Kimura, M Shirasu, C Wong, C Kadooka, P Kim, J Betwee, T Smith, G Goto, J Lumeng, A Kunitomo, J McDonnell, W W L Dang; F Reppun, Editor, HMJ; Legal Counsel Vernon Woo; Auxiliary representative, S Foo; medical student M Rivera; HMA Staff: J Won, B Kendro, L Tong, N Jones, J Estioko and A Rogness, recording secretary.

President Jeanette Chang reported on a most successful visit to Washington, DC, for the AMA "New Partnership" meeting with high-ranking White House and Congressional people to get medicine's message across on health-care reform to include free choice of physician, insurance coverage for all and the inclusion of practicing physicians in the planning and implementation of health care reform. Encouraging messages were heard from Vice President Al Gore, Senate President George Mitchell, House Minority Whip Newt Gingrich, and those deeply involved in health care reform—Senators Robert Dole, Ted Kennedy, John Rockefeller and Representatives Pete Stark and Don Nickels. In order to present medicine's positions and Hawaii's need for continued exemption from federal mandates, visits were made to Representatives Neil Abernethy and Patsy Mink, and to Senator Daniel Akaka.

The Auxiliary reported that it had published a 2-page ad

honoring physicians on Doctors' Day, March 30 and had distributed of some 4,000 Doctors' Day buttons. They gave first-aid kits to all legislators. The Council was also reminded of the May 23, 1993 fashion show for the benefit of the Waianae Health Academy.

The Council adopted a position in opposition to a House Concurrent Resolution which calls for arbitration between physicians and nurses for nurse prescriptive authority. It was agreed it was inappropriate to mandate such action, especially when there could not be any compromise in the quality of care delivered to patients.

The registration fee structure for the 1993 HMA Annual Meeting in Kapalua, Maui, was adopted with one change which set a \$50 registration fee for nonmember medical students and residents with the stipulation the fee would be waived if the student or resident joined HCMS and HMA at the time of registration (dues payable by students and residents for HCMS and HMA are waived).

Councilors were reminded that when testifying in hearings before the legislature, they should make it clear as to whom they represent in order to avoid any misunderstanding as to whether they speak for the HMA or for some other organization.

Fred Holschuh
HMA Secretary



Native Hawaiian Medical Lore

We are pleased to be able to include in this issue of the *Journal* a brief article by a second-year student of the John A Burns School of Medicine at UH, Bradley E Hope. He has done research on just 4 out of some 58 medicinal plants known to the Hawaiian Kahunas of old (a few still extant and practicing). Under the tutelage of pulmonologist Doug Massey at Kuakini, Hope has written "Hawaiian *materia medica* for asthma."

He has delved extensively into the literature as evidenced by the list of references. What is unusual, however, is the fact that he also has interviewed one of the remaining living *kahuna lapa'au*.

In these days of the resurgence of so-called "Native Hawaiians" and their culture (the U.S. Congress has defined Native Hawaiian as anyone with Hawaiian blood who can trace his or her lineage to pre-1778, after which racial intermixture with nearly every foreign ethnic peoples took place as the Hawaiians spread their aloha to all comers), it is important from a medical point of view to examine the lore that these Polynesians had. The original inhabitants of *Hawaii nei* were highly intelligent and quite knowledgeable in terms of the human body and how it reacted to illness and injury.

We ourselves were fortunate in having spent nearly 8

years on Molokai after WWII, when there were many people of full Hawaiian ancestry still living as elders in that relatively isolated community; fortunate in that we could talk to them freely in the physician/patient relationship about non-Western medicine. Many of these elders remembered the lore that had been passed down from generation to generation through the spoken word. We often wished we had had the nerve to sneak in a wire or tape recorder unbeknownst to the raconteur! Nor did we have the free time to record on paper what we had heard and learned, *auwe!* Many of these medically knowledgeable elders are now long gone.

It is indeed a coincidence that we are able to include in the same issue of the *Journal* a book review of *Polynesian Herbal Medicine* by ethno-botanist Dr Arthur W Whistler of the National Tropical Garden at Lauwai on Kauai, published this year. Medical student Hope probably hasn't had access to it yet.

Bradley Hope may have started something. We hope his treatise will stimulate others to do some more research on Hawaiian medicinal plants as they relate to the modern western armamentarium.

The Editor

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Book Report

Polynesian Herbal Medicine

Whistler, Dr Arthur W, *Polynesian Herbal Medicine*, Everbest Printing Co., Hong Kong

This is a 1992 publication with beautiful color illustrations of medicinal plants of Polynesia, their local and scientific names, descriptions and use by native healers.

With the resurgence of *Kanaka maoli* culture in recent years and the current Congressional financial stimulus toward reversing the alleged morbidity and greater mortality among our people with Hawaiian blood in their veins, physicians of Hawaii would do well to secure a copy for themselves, to be read and to be on hand for ready reference in the practice of medicine.

In 1868, the Board of Health of the Hawaiian Kingdom legalized the status of the *Kahuna La'au Lapa'au* by licensure with the stipulation that the *kahuna* keep meticulous records of the patients he saw and treated. The heyday of the native medical practitioner was reached by this action, after which it gradually declined to the point of there being, in 1946—some 70 years later—only two in existence who were licensed to practice.

We wonder if there are any at the present time. However, we do know that there still are *Kanaka maoli* healers, to whom many with Hawaiian blood still go. For the most part, they practice healing of the *ma'i 'aumakua*, or illnesses of the spirit that may or may not be associated with the *ma'i kino*, or physical ailments. These practitioners are largely the *kupuna*, elders and laypersons.

The author of this book comes with imposing credentials. He has been with the National Tropical Botanical Garden (NTBG) since 1983 and on the faculty of the University of Hawaii's Department of Botany. NTBG includes 4 gardens: 3 of them in the Hawaiian islands and one in Florida, plus 3 preserves. Whistler has spent 20 years in the various archipelagos of Polynesia, collecting and photographing specimens, reviewing the literature on medicinal usage and interviewing more than 75 "healers" throughout Polynesia.

The book makes for fascinating reading of its first 3 chapters—half the book. Chapter 4, the second half of the book, is totally devoted to the descriptions of the 45 plants reported to be of medicinal value, each one depicted in brilliant color. There are tables and listings by common local names and by scientific names covering Tonga, Samoa, Tahiti, the Cook Islands and Hawaii, such that any researcher can quickly leaf to a particular plant in question. The bibliography is extensive.

Chapter 1 gives an excellent review of the origins of the peoples of Polynesia.

Chapter 2 is an extensive treatise of the status of medical knowledge and practice throughout Polynesia pre-western contact—pre-Cook for Hawaii.

The difficulty in assessing the medical knowledge and practice of the pre-Cook Hawaiians is accentuated by the

absence of any written Hawaiian language of that time. The reports by the westerners who came to the Pacific were sketchy, not done by medical professionals; therefore, without a medical focus, and when recorded by the few professionals, were done through western eyes. Dr Holman, the first physician to settle in the Islands, came in 1820, some 50 years after Captain Cook.

On the basis of this research, therefore, Whistler feels that the Hawaiian medical lore pre-Cook must have consisted primarily of using medicinal plants externally, the reliance being essentially on the effects of incantations. It is granted that the Hawaiian people were basically very healthy, that there was little illness, little infection and that medical care was applied primarily to the injuries suffered from internecine warfare and accidents. There was also an emphasis on *ma'i 'aumakua*, the loss of inner *mana* by the patient, and the need for incantation to the gods to restore *pono* to the suffering patient. Whistler's conclusion, therefore, is that taking potions internally was not in the *kahuna lapa'au's* usual armamentarium. It was noted that those potions were usually mixtures that were foul enough to convince the patient he had better get well fast in order to avoid a second dose!

The native Hawaiian learned men, *Kamakau*, *I'i* and *Malo*, who began to record Hawaiian medical lore, did so some 60 years after the white people had arrived and taken over. By that time, the *kahuna lapa'au* had surely begun to emulate western medicine and, therefore, became the *kahuna la'au lapa'au*—the dispenser and prescriber of medicinals from plants and herbs, primarily the emetics and cathartics, but no longer fearful of giving them internally.

This is a new and interesting piece of knowledge. Another such gem was Whistler's revelation that the early Hawaiians were the only Polynesians who developed the use of the medicinal enema—*waiiki* (on Molokai, the word was *upii*)—and this apparently came about some 70 years post-Cook. The cathartics were: Seawater taken orally initially and if that didn't work, the medicinal plants *moa* (psilotum), *koali* (morning glory) and *kukui* (we know that the delicious flavoring spice *inamona* made from the kukui nut and available at luaus, if taken to excess, is indeed a powerful cathartic!).

Of note also is Whistler's emphasis on the date 1804, when the Hawaiian population was decimated by the epidemic of *'oku'u* (literally the violent excretion from the anal orifice—intractable diarrhea), which was thought to be the result of typhoid fever or perhaps cholera. That and the overthrow of the traditional Hawaiian religion in 1819 Whistler believes caused the remaining Hawaiians to back away from their traditional concepts of healing and pay greater heed to western therapies for illness.

In Chapter 3, Whistler described what followed: In the next 50 years, both systems co-existed in spite of the influence of the Christian missionaries who came to Hawaii from 1820 on and belittled what appeared to them to be the heathenish practices of the natives.

Whistler also in this chapter compares what went on in the various archipelagos of Polynesia as a result of Western influence. It was interesting to be told that Tonga was the

only Polynesian entity that preserved its independence and its own culture in Polynesia, was not subjected to colonization and never became a minority people in its native land.

This is what he has to say about the present day Hawaiian (part-Hawaiians for the most part): Although western medicine plays a major role in the health care of Hawaiians today, and nearly all Hawaiians at some time or another see a doctor, there is still a lingering reluctance among many of them (particularly those who have a strong ethnic identity) to visit doctors. Many Hawaiians avoid doctors except when their condition is very serious, and by then it is sometimes too late for anything to be done."

Whistlers' *Polynesian Herbal Medicine* should be read by every student graduating from the John A Burns School of Medicine in Hawaii.

Erratum:

In the October issue of the *Journal* Vol. 51, No. 10: 269, there was a grave error in attorney Jeff Crabtree's article on the Health-care Power of Attorney. The paragraph should read:

The person appointed as proxy is allowed to make the ultimate decision that will result in the patient's death: the decision to withdraw or withhold life-sustaining medical treatment such as tube feeding, hydration, or surgery. However, the proxy can make this decision only if such authority is explicitly set forth in the patient's health-care power of attorney document. If no such specific wording appears, then it shall be presumed that the patient did not authorize the proxy to withdraw such forms of life-sustaining medical treatment.

We apologize this error occurred—an apology does not rectify it but regular readers might be made aware of the import not in the last sentence of that paragraph.

Editor

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Hawaiian *materia medica* for asthma*

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A literature search and traditional narration determined that at least 58 herbs with scientific names were commonly used by Hawaiians for asthma. Of particular note were Piper methysticum, solanum americanum, and Aleurites moluccana with oral tradition singling out Sophora chrysophylla. These four therapeutic agents, especially Sophora, have scientific merit and warrant further investigation because of the recent increase in asthma mortality, their potential for improved patient compliance, minimal of side effects, and the low cost.

Introduction

In traditional Hawaii, illness or *ma'i* was caused by a loss in *mana* (energy, power) and of *pono* (balance). Return to normal levels of *mana* and of *pono* was sought through holistic methods, which included religious ceremonies, psychospiritual seances, massage, and *materia medica*^{1a, 2a}. A comprehensive review is available³.

Plant products were prescribed by the traditional Hawaiian physician, the *Kahuna la'au lapa'au*, and by knowledgeable commoners. *Kahuna* knowledge, skills and attitudes were passed from generation to generation through oral tradition. There is evidence that the *kahuna* used scientific methodology⁴ which extended to performing autopsies to determine the cause of death.

Following western contact in 1778, the activities of the *kahuna* were suppressed, as were all aspects of Hawaiian culture, and relatively little remains of the knowledge and experience of the pre-Captain-Cook days. Some of this oral tradition does persist with certain practitioners.

The oldest published account of the Hawaiian *materia medica* was printed in the Hawaiian newspaper *Ka Hae Hawaii* in the mid-1800s; it was recently translated to English by Chun^{1a}. Practitioners were meticulous regarding preparation, dosages and observation for side effects⁵.

Turning now to the specific problem of asthma, Hawaiians have always been reported as having the highest asthma mortality per 100,000 ($p < 0.01$) compared to other ethnic groups in Hawaii⁶. In fact, Krauss notes "The

Hawaiians seem to have suffered frequently from respiratory ailments since there are many cures recorded for these"⁷. Neither was royalty spared; in 1863, Alexander Liholiho, known as King Kamehameha IV, died of asthma⁸.

Given the severe and increasing asthma mortality of the 1980s and 1990s in Hawaii, we have reviewed the Hawaiian *materia medica*, especially the written to determine if selected asthma medications should be further examined by scientific trials.

Materials and Methods

Two sources were consulted: the literature and well-respected, practicing Hawaiian healers. The literature search revealed herbs used by Hawaiians for asthma or *hano*. The Hawaiian and scientific names as well as selected illustrations, preparation techniques, and chemical constituents were specified.

Matching scientific names with Hawaiian names was mainly based on Wagner et al^{9a}; Nagata¹⁰; Gutmanis¹¹; Handy et al⁵; Bushnell et al¹²; Abbott and Shimazu¹³; Degener et al¹⁴; and Porter¹⁵. Abbott¹⁶ and Mehrhoff¹⁷ verified all scientific names. Classification of plants whether native, indigenous or introduced into Polynesia was provided by Abbott and Shimazu¹³, by Wagner et al^{9a} and others.

One Hawaiian healer¹⁸ was questioned about the herbs used for asthma and said her expertise was based on oral tradition dating back to 800 AD.

Results

A. Herbs in the literature

Fifty-eight herbs were well documented as having been used for the treatment of asthma in Hawaii (Tables 1a-1c). Some medications were used in combination such as *Ipomoea cairica* and *Argyrea tilia* which called for a laxative to end the treatment. Certain plants have not been included because they do not have a scientific taxonomy equivalent eg, *kalaipahoa*¹⁹ and *lauhulu*⁵.

B. Herbs in the oral tradition

Much of the ancient *materia medica* for asthma is unpublished ie, it is anecdotal by word of mouth. *Sophora chrysophylla* is one such medication.

C. Preparation of medication

Although not all the references provided herbal preparation procedures, a typical example is from *Kaaiakamanu* and *Akina*¹⁹.

"This tree, [*Cheirodendron trigynum*], has bark which, if mixed with other remedies, is effective for a bad case of asthma. This remedy may be prepared as follows: Take the bark of 4 *olapa* roots, the bark of 4 *Waltheria americana* [W.

(Continued on page 162) ►

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indica] roots, the bark of four popolo roots, a piece of the koa bark, 4 *Morinda citrifolia* fruits, a hatful of the leaves, flowers and fruits of the popolo, and two segments of white sugarcane. Have these materials thoroughly pounded together and the juice pressed out and strained. The patient then takes a mouthful of the liquid each morning and evening. *Campylothea* – *bidens* tea should be used regularly with *Psilotum triquetrum* (now known as *P. nudum*) as drinking water.”

D. Posture during treatment

According to Handy et al⁵, respiratory treatments were taken with the patient lying prone in the lordotic position.

E. Scientifically documented Materia Medica

Many of the 58 herbs are not documented scientifically but some are: four of these are now considered in detail.



Figure 1: *Piper methysticum*, 'awa

Piper methysticum – 'awa, kava

• Botany: (Fig 1¹⁶) Piper is a pantropical genus comprised of more than 2,000 species. It was introduced to Hawaii by Polynesians, grows as a shrub 1.5 to 3 meters tall, and is found at an altitude of 50 to 500 meters on all major Hawaiian islands except Kaho'olawe, Ni'ihau and Lana'i^{9b}.

• Chemistry: It contains 7 major and 8 minor lactones or kavalactones. Among the former are kawain, dihydrokawain, methysticin²⁰, dihydromethysticin, yangonin²¹, and tetrahydroyangonin²²; also found are benzoic acid and cinnamic acid^{23a}. A more detailed review of research on *kava* is provided by the South Pacific Commission^{24a}. The chemical structures of kawain, methysticin, and yangonin^{24b} are known.

• Pharmacology: Anti-inflammatory properties are exhibited by dihydromethysticin, methysticin, dihydrokawain, kawain, and yangonin. Dihydromethysticin and dihydrokawain are muscle relaxants^{25a}; benzoic acid is an expectorant^{25b}.

• Toxicity: Piper depresses the central nervous system²⁶ and may cause inflammation of eyes and skin^{25c}.

• Therapy: Asthma^{19,27}.

• History: *Awa* also was used as a mildly intoxicating beverage and for religious ceremonies^{2b}.

Solanum americanum – popolo, glossy nightshade

• Botany: (Fig 2.)¹⁶ Indigenous popolo is a plant that reaches

(Continued on page 164) ►

TABLE 1a - HAWAIIAN MATERIA MEDICA USED FOR ASTHMA

BOTANICAL	HAWAIIAN. COMMON	SOURCE	FORMAT
Acacia koa gray ^{19,34}	KOA	I, E	B
Aleurites moluccana ^{19,11,5,1b}	KUKUI, candlenut	P	B, F, nut
Argemone glauca ^{19,11}	PUAKALA, prickly poppy	E	F, B, R, NS
Argyrea tilia ¹⁹	PILIKAI	X	NS
Artemisia australis ^{19,11}	'AHINAHINA, Oahu wormwood	E	L, T, R/tea
Asplenium nidus ¹⁹	'EKAHAKAHA	I	S, R, NS
Bidens spp ¹⁹	KO'OKO'OLAU	E	St, Bd, L/tea, F
Capsicum annum ¹⁹	NIOI, chili	X	NS
Carica papaya ¹⁹	HE'I	N	Fr
Chamaesyce multiformis ¹⁹	'AKOKO	E	L, Bd
Cheirodendron trigynum ^{19,34}	'OLAPA	E	B, R
Cinnamomum camphor ¹⁹	PILALI	N	NS
Clermontia arborescens ^{19,10}	'OHA-WAI-NUI	E	Sh,Fr
Cocos nucifera ¹⁹	NUI, coconut	P	Fr, milk
Colocasia esculenta ^{19,5}	KALO, taro	P	L,NS
Cordyline fruticosa ¹⁹	KI or TI	P	F, L, R, S
Curcuma longa ¹⁹	'OLENA, tumeric	P	Bb, tuber
Cyperus laevigatus ¹⁹	MAKALOA	I	Fibres, tea
Datura stramonium ¹⁰	KIKANIA, jimsonweed	X	L
Desmodium uncinatum ^{19,34}	PUAPILIPILI	X	L, smoke
Digitaria setigera ¹¹	MAU'U KUKAE PUA'A, itchy crabgrass	I	grass

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1.2 meters in height and grows from sea level to an altitude of 2,380 meters. It is found on all Hawaiian Islands and neighboring atolls^{9c}.

• Chemistry: Although its active chemical components are unknown, studies of closely related plants such as *S. nigrum* may provide clues. The immature fruit of *S. nigrum* contains steroidal glycosides and alkaloids²⁸. The alkaloids of the Genus *Solanum* include solanidine, solanine²⁹, and solasonine, which can be converted into solasodine, and thus be used to manufacture steroidal drugs^{30,31,32}. The chemical structure for solanine and solasodine are known^{33a}.

• Pharmacology: Solanine has antihistaminic properties, perhaps from its steroidal properties, and solasodine is an anti-inflammatory agent^{25d}.

• Toxicity: No side effects are documented for *S. americanum*, but toxicity of *S. nigrum* includes coma, paralysis, diarrhea, and rarely respiratory death^{25e}.

• Therapy: Asthma^{19,34}.

• History: Popolo was used for food^{2c}.



Figure 2: *Solanum americanum*, popolo

Aleurites moluccana – kukui, candlenut

• Botany: (Fig. 3)¹⁶ Found in tropical areas worldwide, *A. Moluccana* is a tree 10 to 20 meters tall. It grows from sea level to 700 meters. Introduced by Polynesians, it is found on all islands except Kaho'olawe^{9d}.

• Chemistry: Alkaloids have been found in the immature and mature fruit³⁵. The bark has 5% tannin and the oil contains glycerides of oleic acid, linoleic acid, and linolenic acid. Other constituents include saponin and phytotoxin^{25f}.

• Pharmacology: Its anti-asthma action may reside in the alkaloids and glycerides.

• Toxicity: Kukui is considered to have intermediate toxicity compared to *A. montana* and *A. trisperma*³⁶, particularly on the gut.

• Therapy: Asthma^{1,5,11,19}.

• History: Hawaiians used the oil for torches and the wood for canoes^{2d}.



Figure 3: *Aleurites moluccana*, kukui

Sophora chrysophylla – mamane, mamani

• Botany: (Fig. 4)¹⁶ The genus *Sophora* is found in temperate and tropical areas from India to the southwest United States and

TABLE 1b - HAWAIIAN MATERIA MEDICA USED FOR ASTHMA

<u>BOTANICAL</u>	<u>HAWAIIAN. COMMON</u>	<u>SOURCE</u>	<u>FORMAT</u>
<i>Dodonaea viscosa</i> ³⁴	'A'ALI'I	E, I	L
<i>Eleocharis</i> sp ¹⁹	KOHEKOHE, spikerush	I	reeds
<i>Eucalyptus</i> spp ¹¹	PALEPIWA	X	B, vapor
<i>Heliotropium anomalum</i> ¹⁹	HINAHINAKUKAHAKAI or HINAHINA	I	R, L, NS
<i>Heteropogon contortus</i> ¹⁹	PILI	I	NS
<i>Ipomoea batatas</i> ¹⁹	'UALA, HUAMOA, sweet potato	P	NS, Bb
<i>Ipomoea cairica</i> ¹⁹	KOALI 'AI	1, X	NS, R
<i>Ipomoea</i> sp. ¹⁹	KOALI	I	Bb
<i>Ipomoea pes-carpae</i> ¹⁹	POHUEHUE, beach morning glory	I	NS
<i>Lythrum maritimum</i> ¹⁹	PUKAMOLE	I	R
<i>Metrosideros macropus</i> ^{19,5}	LEHUA	E	L, B
<i>Monostroma latissimum</i> ¹⁹	LIMUPAHAPAHAKAI, seaweed	I	NS
<i>Morinda citrifolia</i> ^{19,34}	NONI, Indian mulberry	P	Fr, B
<i>Musa x paradisiaca</i> ^{19,5}	MAI'A, banana	P	R, F, Fr, L
<i>Myoporum sandwicense</i> ¹⁹	NAIO	E, I	L, Bb, F, Fr
<i>Nasturtium officinale</i> ¹⁹	LEKO-'ELE'ELE, watercress	X	NS
<i>Oxalis coriculata</i> ¹⁹	'IHI'AWA, yellow wood sorrel	P	NS
<i>Pandanus tectorius</i> ^{19,11}	HALA	E, I	L, S, R
<i>Peperomia latifolia</i> ¹⁹	'ALA'ALAWAINUI	E	Bd, St, Fr, F, L
<i>Piper methysticum</i> ^{19,27}	'AWA, KAVA	P	L, B, R

is comprised of about 50 species. Mamane is endemic to Hawaii and, although usually a shrub, it may reach 15 meters in height; it grows at altitudes of 450 to 3,240 meters. It is found on all islands except Niihau and Kaho'olawe^{2a}.

- Chemistry: *S. chrysophylla* contains quinolizidine alkaloids including anagyrine, cytisine, matrine, sophoramine³⁷. It also contains flavonoids and glycoproteins. The chemical structures of cytisine and matrine are known^{33b}.

- Pharmacology: Cytisine has anti-inflammatory properties and matrine suppresses some of the interleukins; both actions are useful in treatment of asthma^{25g, 25h}.

- Toxicity: There is no documented toxicity to *S. chrysophylla* although other *Sophora* species may rarely be associated with side effects from their alkaloids eg. *S. flavescens* ait with its matrine and *S. secundiflora* with its cystisine. The former in pure intravenous form has been associated with mild anaphylactic shock in one patient and the latter with nausea, convulsions, and asphyxia^{23b}.

- Therapy: Asthma¹⁸.



Figure 4: *Sophora chrysophylla*, popolo

- History: Mamane also was used for constructing sleds and digging sticks^{2d}.

Discussion

New Findings

Numerous plants in the Hawaiian *materia medica* were used for asthma. Several, such as *Sophora flavescens* ait, have been well documented scientifically and could be considered for Phase I clinical trials.

Limitations

This review of the Hawaiian *materia medica* as a guide for future cost-effective research into its members has limitations. Although all sources specifically referred to asthma or *hano* as the ailment treated, the authors' exact definition or even understanding of asthma were not given. However, many such as Handy et al⁵ associate *hano* with cough, wheeze and difficulty in breathing. Even today a universally accepted definition for asthma has not been formulated.

Certain authors were not precise in listing their original sources of information about the specific plants. There are some inconsistencies in matching scientific names with Hawaiian names; some Hawaiian plants have not yet been assigned a scientific name. A botanical authority, Dr I A Abbott¹⁶ and a research botanist, L A Mehrhoff¹⁷ minimized these differences.

Assigning a definite time period as to when these tradi-
(Continued) ➤

TABLE 1c - HAWAIIAN MATERIA MEDICA USED FOR ASTHMA

BOTANICAL	HAWAIIAN, COMMON	SOURCE	FORMAT
Pleomele aurea ¹⁹	HALAPAPE	E	R, B, L
Portulaca oleracea ¹⁹	pigweed	X	NS
Psilotum triquetum ¹⁹	MOA	I	NS, L, seed
Rumex giganteus ¹⁹	PAWALE	E	S
Saccharum officinarum ^{19,34}	KO, sugarcane red, white	P	S
Sadleria spp ^{19,34}	'AMA'UMA'U	E	T, S, St, NS,tea
Santalum spp ¹⁹	'ILIAHI, sandalwood	E	L, Bb, stem
Sida fallax ¹⁹	'ILIMA	E, I	NS, B, S, R, F
Solanum americanum ^{19,34}	POPOLO, glossy nightshade	I	L, B, R, Fr, Bb,F
Sophora chrysophylla ¹⁸	MAMANE	E	NS
Stenogyne scrophularioides ¹⁹	MOHIHI	E	NS
Syzygium malaccense ¹⁹	'OHI'A'AI, mountain apple	P	NS, B
Ulva fasciata ¹⁰	LIPALAHALAH	I	WEED
Vigna marina ¹⁹	'OKOLEOMAKILI, beach pea	I	Bb, L, F, NS
Waltheria indica ^{19,5,34}	'UHALOA, HI'ALOA	I	Bb, B, R, L, F, tea, smoked
Wikstroemia oahuensis ¹⁹	'AKAI LAU-NUI	E	NS
Xanthium strumarium ¹⁰	KIKANIA	X	L

B= bark; Bb= bulb; E= endemic; F= flower; Fr= fruit; I= indigenous; L= leaf; N= naturalized;

NS= non-specific reference; P=Polynesian introduced; R= root; S=shoot; Sh= shrub; T= trunk;

X= not native (post-1778).

tional remedies were used is difficult. The oldest printed description of the oral tradition was published in the mid-1800s. Unpublished oral traditional herbal use may reflect more closely the Hawaiian traditional *materia medica*; the use of certain herbs has been traced back to AD 800.

Furthermore, we have no way of knowing whether a certain medicinal herb contained active ingredients, was used solely for the purpose of making the herbal preparation more palatable, or to reduce side effects. Certainly some were of questionable efficacy⁵.

It has been found that the degree of pharmacological activity of *awa* varied with geography, techniques of cultivation, types of preparation, and the presence of other chemicals^{24a}.

Implications

Despite the excellence of the western therapeutic approach to asthma, it is not without inadequacies, especially in its inability to control the mortality epidemic of the 1980s and 1990s in Hawaii. On the other hand, the Hawaiian *materia medica* shows potential advantages such as cultural acceptance and lack of side effects, both tending to improve patient compliance. In addition, the cost of medication is often only a few cents a day.

At least 2 of the Hawaiian *materia medica* should be investigated in greater depth. *Aleurites moluccana* or kukui was mentioned in 4 independent written sources and 1 oral. *Sophora chrysophylla* is even more promising, not only because of previous scientific investigations, but the results of cell culture, animal, and clinical investigation of *Sophora flavescens* ait may be extrapolated to this local medication³⁸.

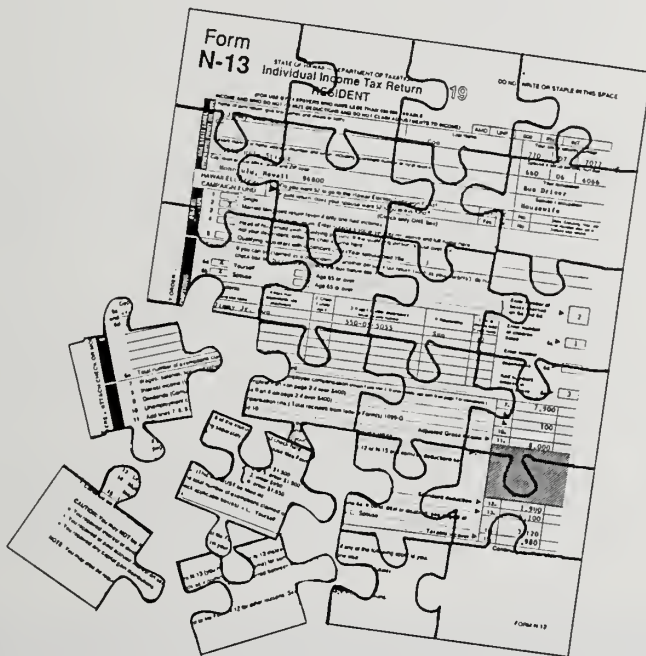
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ADHD Revisited: A whimsical review

Robert G Dimler MD*

Bob Dimler is a long-time plantation physician and pediatrician with the Honolulu Medical Group in its Kailua Branch when that existed. After his retirement from active practice he volunteered for many years at Kokua Kalihi Valley Comprehensive Family Health Center.

The Editor

Late in the 19th century a behavior disorder, with or without hyperactivity, was labeled as a brain-damage syndrome, the result of a central nervous system infection, a head injury, or brain insults.

Then in the period 1930 to 1940, there arose the idea that this syndrome in itself could be secondary to brain damage.

In the 1960s, the syndrome of Attention Deficit Hyperactivity Disorder (ADHD) without accompanying brain damage was considered and labeled as Minimal Brain Damage. It appears that the stigma of brain damage never left the picture.

In 1968, Learning Disability finally was separated from ADHD, although the entire syndrome ADHD/LD exists rather commonly.

Over the years the proportion of boys to girls decreased from 8:1 to 5:1.

All physicians, regardless of specialty or subspecialty, are familiar with the use of stimulants in the multidisciplinary approach to ADHD. Methylphenidate and dextroamphetamine continue to be of value, with methylphenidate in the forefront and pemoline a distant third.

Seventeen side effects, many of them transient or dosage affected, have been attributed to methylphenidate. In one report the author does his best to repudiate most of them. Physicians familiar with the drug are cognizant of many of these and the relative transience of most.

The recommended provisional dosage of methylphenidate is to begin with 0.3 mgm/k b.i.d. and increase to 0.8 to 1.0 mgm/K b.i.d. Dosages in excess of 1.0 mgm can increase symptoms and side-effects. Occasionally a t.i.d. regimen may be indicated. Older children can tolerate 40 to 60 mgm a day.

It is interesting to note that in England methylphenidate is not prescribed. This may not be true at present, however.

Dextroamphetamine can, as a rule of thumb, be beneficial at one-half the suggested strength of methylphenidate. Children 3 to 5 years old can start with 2.5 mgm daily with the dose if needed, increased by 2.5 mgm daily each week. Children 6 and older may start with 5 mgm per day; the daily dose can be increased step-wise by 5 mgm if needed.

Cylert (pemoline) chewable tablets are available in 3 strengths: 18.75, 37.5 and 75 mgm. Treatment is begun with

37.5 mgm and, at one week intervals, gradually increased by 18.75 mgm. The maximum advocated dose is 112.5 mgm; however, such a dosage would be for older children. Periodic monitoring of the hepatic profile is recommended.

The use of methylphenidate in the usual b.i.d. dosage has been reported to result in a "window" of increased cognizance of but one to 3 hours after ingestion. This can result in a therapeutic dip. Therefore, perhaps Methylphenidate SR-20 (the equivalent of 10 mgm b.i.d.) could be preferable from 2 standpoints: only 1 a.m. dose with an effect coming on 2 hours after ingestion and lasting about 9 hours. This is in accordance with one report.

This same study relates the equivalency of Methylphenidate SR-20, Dextroamphetamine spansules-10 (to be swallowed whole), and Cylert. There is some evidence that dextroamphetamine, compared to methylphenidate, may result in more side effects.

Current information from the American Psychiatric Association on the treatment of psychiatric disorders cites the pharmaceutical treatment of ADHD as follows: After 2 weeks of maximum dosage of dextroamphetamine and then methylphenidate or 5 weeks of pemoline without demonstrable benefit, cessation of therapy is recommended. Then their choice would be a tricyclic antidepressant, namely imipramine or desipramine at a dosage of less than 5 mcgm/k/day (usually about 100 mgm/day in divided doses). Cardiac monitoring is essential with this regimen.

Clonidine has been used with some success at an oral dose of 5 mcgm/k/day; q.i.d. blood pressure must be monitored. The same *APA Bulletin* stresses the vast importance of the multimode treatment, including all disciplines likely to be involved.

Imipramine and desipramine follow identical metabolic pathways. The use of imipramine for night enuresis seems to have fallen into disfavor. As an antidepressant, it should be reserved for adolescents aged 18 and above. In any case, it may be wise to limit its use on children ages 5 or 6 or older. Its use in prepubescent children is contraindicated because of suspected possible permanent defects in cardiac conduction systems.

According to the author of *Pediatric Notes*, certainly imipramine and one of the stimulants should not be used concomitantly. Recently, the 1975 ogre of Sudden Infant Death secondary to imiprimine was refuted. Contrarily, a report claimed more or less the opposite.

Hard on the increase in use of stimulants in treating ADHD was the appearance of much criticism, especially from the Church of Scientology with its Citizens' Commission for Civil Rights. Threatened suits against some 600 physicians appeared, claiming use of "clinical billy clubs and straitjackets"; claiming that prescribed stimulants resulted in murder, suicide and drug-abuse.

Today remnants of these vociferous claims are found in

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the emphasis on natural, herbal or nutritional remedies; on the close inspection of every supermarket item for the presence of food additives or supplements. This approach to ADHD has its place, but in a proper perspective.

Drug therapy is one arm of the needed multidisciplinary approach to the diagnosis of ADHD with or without LD. The child's school provides the cornerstone of the locus. The Connor scale used in the classroom for rating a pre-school or elementary student as having a probable ADHD is an excellent determinant. It is preferable for this be used twice and by 2 separate teachers. Then the child should be tested psychologically, and thoroughly so. Needed is a consultation with the primary physician regarding past and present medical history, pertinent family history and whether medication is needed and when.

A social worker is a vital fourth arm of the team in evaluating home and social environs. It would not be unusual for a child to be labeled with ADHD when, in truth, his class behavior and inattention comprise a pseudo-ADHD, totally secondary to a deplorable, devastating family and social environment.

At this point, perhaps a loose recital of my impressions may be practical in terms of the etiology of ADHD, with or without learning disability, although oftentimes the two are aligned, eg, ADHD/LD:

(1) **Inborn:** In adults observed with ADHD, according to one study, each had at least one child with ADHD. One report suggests that of 20 children with persistent ADHD, 2, when adult, will continue to ride in the saddle of ADHD.

(2) **Family Environment:** Psychosis must be excluded. Subclinical Tourette's disease should also be differentiated.

The most common family/social degrading influences hysteria, alcoholism, drug abuse, child and/or spouse abuse, including sexual and parental indifference.

(3) **Neurological:** One must differentiate ADHD from post-encephalitis, personality change as an indicator of organic brain disease, subclinical epilepsy and hypothyroidism (now routinely checked at birth).

(4) **Toxins:**

a. Lead poisoning is high in the top 10 on the toxicology list despite illegal lead-based paint and the marked decrease in the use of leaded gasoline. Old houses painted with a lead base still stand.

A recent report suggests that toddlers with foreign bodies in the nose, ears or the gastrointestinal tract are much more apt to indulge in pica which, in turn, occurs more in low-income families; who, in turn, are more often apt to live in houses that have had lead-based paint only partially removed.

If children with significant lead in their blood have a routine flat plate of the abdomen taken, radio opaque flakes of lead are apt to be seen.

In summary, 16% of American children have lead levels in the neurotoxic range. Significant exposure to lead affects intelligence, neurologic behavior and cognitive function. It has been said that lead toxicity can be found with levels as low as 10mcgm/L. In screening for levels, it is suggested that if lead levels between 10 and 40 are found, the tests should be repeated every 3 weeks until the levels come down to below 10 mcgm/L.

Chelating agents for laundering lead levels such as

(Continued) ►

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EDTA are expensive and time consuming. It is still uncertain if they are of true, lasting benefit. Penicillamine also is used, but its long-term effect still is unknown. A new oral-chelating agent, Succimer, is awaiting favorable or unfavorable reports. In the present high-tech age, when lead levels are less than 25 mcgm/L, no beneficial treatment seems to be on the therapeutic horizon.

Treating lead poisoning is not the answer. Eliminating the sources of the toxin is the obvious task. At present, lead-contaminated dust and water are the principal agents. Old lead-paint-contaminated houses in low-income areas are a not-too-distant third. It seems clear that lead-poisoning lurks at all levels of childhood society and even the affluent no longer can be secure.

Modern medicine routinely requires newborns to be tested for PKU (a rare disease) and for thyroid metabolic function. We check for sickle-cell disease, the thalassemias, and do routine hematocrits; and yet, we ignore routine screening for lead-levels.

(b) **Fetal Alcohol Syndrome** may lead to ADHD/LD. Fetal exposure to drug abuse, especially cocaine may have a permanent effect as yet not clear, but may be extrapolated to permanent CNS damage.

(5) **Anemia:** Lassitude and inattention are the result, generating learning disability. Rarely is there hyperactivity unless in aggressive response to scolding by parent or teacher.

(6) **Sensory Disorders:** Decreased hearing and vision can be detected in compulsory school physicals.

(7) **Allergies:** Food substances and additives have their strong and their mild advocates. There seems to be little doubt that the elimination of certain foods and food additives can result in a diminishing of substantive effects of ADHD.

Several years ago, Dr. Feingold studied food allergies relevant to ADHD. There are 20 *guilty* foods on his list, plus all food additives, chocolates, toothpaste, and all medications containing salicylic acid.

Adherents to the regime profess success. There is the majority who include allergies as part and parcel of the whole. It would seem proper to suggest that there are varying degrees of ADHD, with or without LD, just as there are varying degrees of Down's syndrome and other entities. Perhaps that is why different regimens of treatment for ADHD, with or without LD, have their start and at times nearly stubborn supporters.

(8) **Maturation Lag:** Very mild cerebral palsy, or a delay in most physical and learning aspects, some of which can be caught up in the early future, can be detected. The pediatrician's growth chart is a needed adjunct to diagnosis and treatment.

(9) **Psychoneurosis:** A good and complete psychological exam is an absolute. Consider subliminal autism. Consider subclinical Tourette's disease such as persistent pre-treatment tic, especially if a parent has the same nervous sign. Lastly, suspicion of a latent psychosis should always be on the examiner's mind, especially if a psychosis is in the family history. There are markers in early onset of childhood schizophrenia; that stigma is a rarity in pediatrics.

(10) **Mild Mental Retardation:** Hyperactivity may be secondary to this syndrome. Here lies the necessity of early

and frequent check-ups by the pediatrician and careful observation by the teacher to establish ADHD/LD on this basis.

Laboratory Diagnosis

(1) **EEG** is actually non-informative unless subclinical epilepsy is suspected.

(2) **CAT SCAN** may show mild cerebral atrophy or reversal of right/left asymmetry. Again, it is equivocal.

(3) **PET** Radioactive glucose was tagged and injected into a cerebral artery in 25 young adults diagnosed as having ADHD. Compared with controls, a statistically significant 8.1% disease in cell uptake of glucose was noted in 3 cerebral areas. These regions affect attention, motor activity and control of automatic responses to certain sensory stimuli, such as hearing, smell and feeling. A few of the sensory changes can be slightly mindful of autism. This experiment probably will be or has been repeated. Other compounds will be tested in this manner. The implications are exciting.

Called to mind is the *old formula* for hyperactivity: 4 tablespoons of powdered glucose a day in divided doses. In deference to whole-body metabolism, it may be judicious to increase considerably the carbohydrate intake.

Now for the bad news

It is thought that if the signs and symptoms of ADHD, with or without LD, persist beyond the age of 8, the syndrome may well persist into adolescence despite treatment and counseling. In the higher grades, unfortunately, few of these adolescents are being treated in any way. If methylphenidate is to be tried, and if there is good compliance, 80 mgm a day can be tolerated.

The statistics: 20% of elementary and intermediate school children with ADHD may be symptom-free when they enter adolescence. Interestingly and comparable to the rule of thumb in allergy: If a child's allergy symptoms persist beyond the age of 13, he will probably have some allergy symptoms on into adulthood. Desensitization in childhood may effect a moderation of this tendency. So it might be with ADHD.

Of the remaining 80% of young people with ADHD (especially with LD), some 30% are destined to be loners, subject to the devious paths taken by those with that syndrome. And of that remaining 80%, 50% are or will be on the road to antisocial behavior. Fifty percent will still demonstrate some learning disability and in these two 50-percentiles, hyperactivity will be persistent, with all its impulsivity, aggressiveness and consequent anger.

If an ADHD youth with antisocial conduct and aggressiveness, combined with impulsivity and abetted by drugs and alcohol, has a gun in his or her hand, what may be anticipated? In 1990 to 1991, the main cause of death in males aged approximately 17 to 22 was murder.

In adults some ADHD symptoms persist to a greater degree, some to a lesser. Old learning disabilities proportionately persist. One ponders this: How many ADHD-persistent adults, men and women, inhabit our prisons, which are bulging at the seams?

Impulsive aggressiveness, properly guided by professional counselors and with continued pharmaceutical treatment, can with effort be turned around 180 degrees. Aggressiveness even in the medical profession can be sublimated, eg from surgery to *fighting* disease; or in community work, such as *fighting for a cause* (crowds of abortion and civil rights demonstrators are a

sum-total of individual aggravations). Firefighters, some athletes, law enforcement officers (incidents of police abuse probably are an overdrive effect—a reason, but not an excuse) manifest this sublimation.

Imprinted on the reverse side of the coin is conscienceless criminality, hand in hand with unrestraint and bloodshed. In this subpopulation, humanism becomes an irritating ghost.

There are subjective signs and symptoms resultant from the ADHD syndrome with or without LD. However, it is unfortunate that often hidden signs and symptoms of the ADHD syndrome are not included or are not noted, or are misunderstood, both by parents and teachers. These traits appear early in elementary school, often regardless of multidisciplinary treatment. These warning signs include:

(1) **Sensitivity.** I would venture that nearly every ADHD child is very sensitive to the actions and words of peers and adults.

(2) **Guilt.** “Why do I have to take medicine and get all these tests?” “Something must be wrong with me, but what?” “No matter what I do, things don’t come out right!” Guilt is the parent of strenuous self-criticism.

(3) **Guilt** and sensitivity breed the ogre of low self-esteem. Trying desperately to live up to expectations of others is unsuccessful because the harder he or she tries, the more he or she gets in his or her own way, making one error, one blunder after another.

(5) **Feeling unworthy** of any praise or even of being loved.

(6) **Depression** is manifested by a loner, plagued by ADHD, with or without LD, who remains in the land of in-between, not antisocial, but longing for the greener grass. Or

by a loner, plagued by ADHD/LD (very likely) who chooses the road of impulsive aggressiveness in adolescence. “I can belong to something; people (the gang) accept me.” The loner becomes a *belonger*, drifting into alcohol and drug abuse. Again, humanism has been lost¹⁴.

(7) **Subjective poor concentration.** This is distinct from extraneous intrusion. Oftentimes subconsciously, the child’s mind wanders into foreign fields while trying to focus on his or her lesson. This mental meandering is to be accepted for what it is, before some type of corrective therapy is attempted. On the other hand, the ADHD child can *lock onto* a television cartoon and will resist interruption. This inconsistency can apply to any subject or person he or she finds of intense interest. Concerned adults have difficulty accepting this incongruity: “If he can concentrate on cartoons, then he can concentrate on his homework!”

Many of these ADHD children possess a credible degree of intelligence, although hampered by a learning disability. An IQ test given by one observer can be misleading. There are too many variants—subjective and objective. The child deserves one or more testings offered by separate professionals. I have noted a deep mental keenness in several ADHD children. If this be so, and if a child finds a certain object to be of intense interest to him or her, one he or she can lock onto, take apart and reassemble, could not his early education be centered on this inherent ability? His or her learning could expand from this base, thus encouraging his or her searching for associated topics or objects.

ADHD, with or without LD, if considered early-on (1% to 5% demonstrate signs and symptoms before elementary

(Continued) ►



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ADHD REVISITED: A WHIMSICAL REVIEW (Continued from page 171)

school age); and, if properly treated with medication and frequent follow-ups and conferences throughout the schooling years (if that be at all possible); and, if these disciplines persist through intermediate and high school; some of these children and adolescents could be salvaged.

It appears to me that the sad record of ADHD, treated or not, in adolescents and young adults could in part be laid at the feet of inconsistent, multidisciplinary checks and *check again*. Unfortunately the early treatment teams cannot track these individuals into and through their teens.

Much — so much — remains to be done. Elementary school reports on ADHD children with or without LD are in confidential files. Some records follow the child into intermediate school. Perhaps the chart is "flagged" in high school; most likely it ends there.

Unfortunately, such a long, ongoing, multidisciplinary management of these problem children would require no less than a social upheaval — nonetheless, a start would be a start. Every journey has a beginning.

I need to make the reader aware that some segments of this article are of biographical origin; other segments come from *my own pocket*. In retrospect, there is little doubt that I had a then-unrecognized ADHD without LD. Reaching further back, the etiology could well have been a mild encephalitis accompanying the Spanish influenza which at that time was striding with cruel feet across the world. The possible effects of this remain in my pocket.

Brief and unannotated bibliography

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Taxoplasma gondii Peritonitis

Willis J Chang MD*

Matthew B Goetz MD**

Toxoplasma gondii most often causes encephalitis in HIV-infected patients¹⁻³; infections of other organs are much less often clinically apparent. In particular, peritonitis caused by T. gondii in an Human Immunodeficiency Virus (HIV)-infected patient has been reported only once previously⁴. Herein we report a second case.

Case Report

A 43-year-old HIV seropositive man presented with fever, intermittent nausea with vomiting and weight loss of 60 pounds over a 6 to 8 month period. He had no significant past medical history. Physical examination was remarkable for cachexia, generalized lymphadenopathy, abdominal distension, hepatosplenomegaly and ascites. The WBC count was $6.0 \times 10^9/L$, platelet count was $151 \times 10^9/L$, and hemoglobin was 9.6 g/L. CD4 positive lymphocyte count was $0.24 \times 10^9/L$. Serology for *T. gondii* (IFA, VA reference laboratory, Lexington, Ky.) demonstrated an IgM=1:160 and IgG=1:128. Computed tomography of the abdomen demonstrated ascites, hepatosplenomegaly, and mesenteric and retroperitoneal lymphadenopathy. Fluid removed by paracentesis showed an RBC count of $5.65 \times 10^9/L$, WBC count of $2.25 \times 10^9/L$ (0.02 neutrophils and 0.98 mononuclear cells), total protein 31 g/L. Cultures and histopathologic evaluations of the ascitic fluid were negative for bacteria, fungi and mycobacteria. A bone marrow biopsy revealed no evidence of infection or malignancy. No therapy was given.

Three weeks later the patient developed diffuse abdominal pain, fever, and chills. The WBC count was $9.9 \times 10^9/L$ with 0.68 neutrophils, 0.30 lymphocytes, and 0.02 monocytes. *T. gondii* titers were now IgM=1:16 and IgG2 1:4096. Repeat paracentesis on admission obtained fluid that showed a WBC

count of $27.6 \times 10^9/L$ (0.89 neutrophils and 0.11 mononuclear cells), total protein was 38 g/L. Again all stains and cultures were negative.

After 4 days of empiric therapy with ticarcillin/clavulanate and gentamicin, the patient defervesced and gentamicin was discontinued. The ascitic fluid then had a WBC count of $2.4 \times 10^9/L$ (0.02 neutrophils and 0.98 mononuclear cells). Stains, cultures and cytology were again negative. Ticarcillin/clavulanate was discontinued after a total of 10 days. Liver biopsy revealed a fatty liver with a moderate portal mononuclear inflammatory infiltrate; cultures were without significant growth.

During the third week of hospitalization, fever, abdominal pain, nausea and vomiting recurred and a 10-day course of ampicillin, gentamicin and metronidazole was initiated. Although CT scan of the head with contrast was unremarkable, pyrimethamine and sulfadiazine were also started. A fourth paracentesis revealed a WBC of $40.0 \times 10^9/L$ (0.65 neutrophils and 0.35 mononuclear cells). Five days later, a fifth paracentesis revealed a WBC of $7 \times 10^9/L$ (0.33 neutrophils and 0.67 mononuclear cells). Cultures and stains from both specimens were negative.

Over the ensuing 3 weeks the patient's abdominal pain resolved and the ascites markedly decreased. Due to the development of a diffuse macular, erythematous rash the sulfadiazine was discontinued and clindamycin was started. By the fifth week of therapy for toxoplasmosis there was complete resolution of his symptoms and ascites. At 8 months the patient continued to tolerate therapy with pyrimethamine and clindamycin without recurrence of the peritonitis. The patient was subsequently lost to follow-up.

Discussion

Despite failure to demonstrate *T. gondii* directly in our patient's peritoneal fluid, we believe that his serologic data and clinical course support the diagnosis of toxoplasmic peritonitis. While the patient did initially respond to antibacterial therapy, suggesting a diagnosis of bacterial peritonitis, his improvement was not complete nor was it long-lasting. In contrast, he responded completely to therapy directed at *T. gondii* without evidence of recurrence for at least 8 months. Furthermore, not only were repeated bacterial, mycobacterial, fungal and viral cultures of the ascitic fluid all negative, but the characteristics of the first paracentesis are more consistent with a chronic peritonitis rather than with spontaneous bacterial peritonitis.

In addition to encephalitis¹⁻³ in HIV-infected patients, *T. gondii* has been reported to cause chorioretinitis^{5,6}, pneumonia⁷, orchitis⁸, myocarditis⁹, hepatitis¹⁰, and, in a single case

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report, toxoplasmic peritonitis⁴. While peritonitis appears to be a rare manifestation of infection with *T. gondii* in the HIV-infected population, this may reflect in part the infrequency with which this diagnosis is suspected.

ACKNOWLEDGEMENT:

Our case report describes a patient seen in Southern California during Dr Chang's Infectious Diseases Fellowship at the UCLA/San Fernando Valley Program. Since there is no Infectious Diseases Fellowship program in Hawaii, Dr. Chang sought fellowship training in Los Angeles.

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Maka O Ke Kauka

Russell T Stodd MD

The vision of the mind supplements the vision of the eye.

Glaucoma, that ancient ophthalmic devil, continues to capture imagination and inquiry. At Duke University, ophthalmic research is underway using an old drug, ethacrynic acid, developed 30 years ago by Merck as a diuretic. The postulate is that the drug can be injected into the eye to make the trabecular meshwork more permeable. Meanwhile at the University of Iowa, a glaucoma gene has been discovered that may be a major break in solving the mystery of how and why glaucoma occurs. Credit for the discovery goes to a patient who walked into the ophthalmology clinic with a genealogy of his glaucoma-plagued family for five generations drawn out on a yellow pad. Blood specimens for 37 members of the family were studied and 21 had glaucoma. All of those affected had a genetic marker, while the other family members did not.

It is dangerous to be sincere unless you are also stupid.

The Families USA Foundation supposedly conducted a survey asking the public what medical specialists such as anesthesiologists and radiologists should earn as a "fair" income. The answer: \$80,000. This survey is absurd on the surface and represents nothing more than an expression of envy which could be extended to any high-earning group. Still the reality is the public believes doctors make too much money. Individual intelligence, the years of study and the expense apparently count for little. Despite all the effort and time that physicians donate—such as making the underfunded Medicaid program work, the AAO's National Eye Care Program, volunteers in inner city and rural clinics—still it is all too easily undone by the media, making doctors the whipping boys. We must recognize that physicians are the easy target about rising health costs.

You do live longer with bran, but you spend the last 15 years in the bathroom.

After collecting data for eight years

on a population of 50,000 women, a Harvard Medical School study reporting in *JAMA* claims that a diet rich in carotenoids may delay or even prevent cataracts. The women who ate vegetables rich in carotenoids (spinach, broccoli, sweet potatoes, winter squash) lowered their risk of developing cataracts by as much as 40% compared with the control group. The explanation offered is that carotenoids protect the lens from oxidative damage. And the *Johns Hopkins Medical Letter* claims that vigorous exercise from two to four times a week reduces a person's risk of developing diabetes by 38%, and we know that aspirin prevents heart attacks. Therefore, if you eat properly, exercise regularly, eschew Tailhook parties and Waco compounds, avoid toxic substances, escape trauma and don't shrivel up with global warming, then eventually you will be sitting in a rocking chair in a retirement home, slowly dying of nothing at all.

Look for the ridiculous in everything and you find it.

On the one hand we have the posing, posturing Ralph Nader, shill for American trial lawyers, vilifying doctors for failure to police the sinners in our midst, and on the other hand we have the Federal courts allowing a rash of antitrust lawsuits brought against physician reviewers and hospital administrators by doctors who have been censured. Supposedly the Health Care Quality Improvement Act of 1986 protects review boards from court challenges in exchange for reporting incompetent doctors to the national data bank. but now the appeals courts have ruled that the law provides only for immunity to pay money damages. Does all this sound familiar? As a natural consequence, doctors do not want to serve as reviewers, a hospital's ability to police its doctors is eroding, and the profession becomes more vulnerable to malpractice suits.

Practical politics consists of ignoring facts.

In the fourth century AD the Roman

emperor Diocletian established price ceilings to control the marketplace; violators were to be executed. The result was hoarding, riots and deaths. Four years later Diocletian abdicated in shame. In 1971 President Nixon imposed wage and price controls across the economy. When the controls were lifted in 1974 medical prices skyrocketed 12.4%. The process is likened to putting a kettle on to boil, then placing your hand over the spout. Once controls are put in, incentives shift to gaming the system for maximum reimbursement, shortages occur, and innovation is stifled. But history and past experience do not influence Hillary Rodham C., for she is telling senators that the administration is leaning toward negotiating "price restraints" with the health care industry. The question is, what else can you expect when a lawyer president asks his lawyer wife to sit down with their lawyer friends and solve a medical-financial dilemma?

The Canadian system has only one fault—it is kind of lousy.

North of the 49th parallel, 80% of Canadian doctors say that the government is wrecking the health care system. Increasing control and manipulation is demoralizing doctors. For example, 96% of doctors in British Columbia are angry and point to a new law that allows the provincial government to establish practice parameters and determine where new physicians can locate their offices. Forty-five percent say they are seriously considering practicing elsewhere.

Addenda

▲ "Towering genius disdains a beaten path. It seeks regions hitherto unexplored."

▲ Familiarity breeds contempt—and children.

ALOHA and keep the faith

rts
■



HENRY N YOKOYAMA MD

Professional Moves

January: Linda Wong, board-certified in general surgery and transplantation, joined the Surgical Associates Inc (Livingston Wong, Fong-Liang Fan, Whitney Limm and Alan Cheung) with offices at Queen's POB II and St Francis Medical Office Bldg.

February: Straub's newest physicians: FP Martina Kamaka at Straub King St and Kailua. OB/Gyn Linda Waki Ho at Straub King St.

More excerpts from *Stitches*

The Journal of Medical Humor-Fall, 1992.

The International Language: Mangled English. Here's a sampling of signs seen in hotels around the world.

Romania: The lift is being fixed for the next day. During that time we regret that you will be unbearable.

Yugoslavia: The flattening of underwear with pleasure is the job of the chambermaid.

Japan: It is forbidden to steal hotel towels please. If you are not a person to do such a thing, please do not read this notice.

Germany: Do not enter the lift backward and only when lit up.

Russia: You are welcome to visit the cemetery where famous Russian and Soviet composers, artists and writers are buried daily except Thursday.

Czechoslovakia: Take one of the horse-drawn city tours—we guarantee miscarriages.

Japan: You are invited to take advantage of the chambermaid.

Switzerland: Because of the impropriety of entertaining guests of the opposite sex in the bedroom, it is suggested that the lobby be used for this purpose.

Italy: Ladies, leave your clothes with the laundry and spend the afternoon having a good time.

France: Please leave your values at the front desk.

Mexico: The manager has personally passed all water served here.

Switzerland: Special today. No ice cream.

Norway: Ladies are requested not to leave children in the bar.

Elected, Appointed and Honored

Talented, personable Tommy Chang, the newly elected chair of the Honolulu Liquor Commission is concerned about selling liquor to minors. "I'd like to see minors get more than a slap on the hand. I think they should be sentenced to community service." Another problem area is that many small bars and retail stores are owned by immigrants with language difficulty who do not always understand what they are

being charged for. "From now on, all managers and bartenders have to attend classes to get registration cards. Our staff will provide 5 hours of training on the rules and state liquor laws." Of the 1,400 liquor licensees, 177 hostess bars get the most attention from liquor inspectors and are the scene of flagrant, illegal behavior such as prostitution and drug dealing. Women are allowed to sit with men customers but are prohibited from soliciting drinks, engaging in lewd acts or consuming drinks. Tommy is understanding, "This is a cultural thing that orientals have had for years. It's like a geisha house: Men want to have female companionship—even if it costs a pretty penny. The problem is when some poor devil who doesn't know the custom, will complain about the costs." Why is Tommy so knowledgeable? His parents ran a bar and restaurant in Wahiawa, and Tommy worked as a bartender during his college years in Omaha, Neb.

Potpourri

Hawaii Honeymoon: "Engaged couples who marry in Japan pay an average \$29,850 for the ceremony, reception and honeymoon trip. The Japanese couples who go to Hawaii to marry pay an average of \$6,400. So report the world wedding watchers." (Lou Boyd, "Just Checking", *Honolulu Advertiser*, March 11, 1993)

Not too hot to Handle

"You like your food hot and spicy, so you order the Mexican salsa designated on the menu with a 3-chili-pepper rating. When you taste it, however, it feels as though your mouth is on fire, so you cool off with a glass of milk. Why milk? It contains a protein known as casein which is particularly effective for washing away the substance in hot peppers that causes the burning sensation. That substance is called capsaicin, and it creates the fiery feeling by binding tightly to taste receptors in the mouth connected to nerve endings that send hot signals to the brain. But the casein in milk, largely by acting like a detergent that literally wipes or strips capsaicin away, stifles the fire," explains Robert Henkin, MD of the Taste and Smell Clinic in Washington, DC. Other possible cooling-off foods, Dr Henkin says, are milk chocolate and several varieties of beans and nuts, but milk is the most effective and is usually the antidote most readily available." (From Mits Tottori's bulletin board)

Hors de Combat

Caffeine and Miscarriage

James Mills, chief of pediatric epidemiology at the National Institute of Child Health and Human Development reports in a February issue of *JAMA* that a study of 431 expectant mothers who consumed 300 mg of caffeine daily, ie 3 cups of coffee, 7 cups of tea or 8 cans of cola, had no higher rate of miscarriages or small fetuses than nonconsumers of caffeine. Earlier studies linking caffeine to birth defects, miscarriages and fetal-growth retardation were defective and are discredited. James adds that "he had no personal desire to exonerate caffeine."

Sex, Age and Hormones (From the February 1993 issue of *Honolulu Magazine*)

The Hormonal Health Care Center from London's Harley Street has opened a branch office on Kapiolani Blvd. The clinic, founded by Malcolm Carruthers, well known, slightly unorthodox medical researcher, provides sex hormones to middle-aged men and women to fight aging. HRT, hormone replacement therapy, is well established for women, but testosterone replacement for men with viropause (the male midlife equivalent of menopause) is not recognized by orthodox medicine. David Wong, CEO says, "It's much like decades ago when male doctors didn't take menopause seriously. We are not saying menopause and viropause are identical. There are some major differences. But that doesn't mean that men have no problems. These men are suffering from constant fatigue, depression, mood swings, loss of memory retention, night sweats, even hot flashes. They've lost their drive at work and their sex drive at home. Their lives are falling apart." David helped his former med school professor Malcolm Carruthers study and treat 1,400 men with low testosterone levels. "We made sure there's a biochemical basis for what we do. Most doctors don't measure the difference between the kind of testosterone your body can use, ie, free testosterone and bound testosterone. The Honolulu Clinic first gives testosterone by injection. If the tests show that the hormone is working, the patient gets a slow-release implant that delivers a 6-month dose. The original testing and the 6-month implant costs \$1,800 but is not covered by HMSA. The clinic also tests for stress and other life-style factors in addition to the rigorous biochemical workup.

Conference Humor

The newly appointed director of IRS was asked by the President to explain the intricacies of the new tax law to the people. So he and his chauffeur drove from city to city, coast to coast, in their government limousine lecturing. After covering about 75 cities, the chauffeur suggested, "I've heard you talk so often that I've got it memorized. Why don't you relax and let me give the next talk." The director, quite exhausted from the whirlwind tour, agreed. "You wear my suit and give the lecture. I'll sit in back in your chauffeur's uniform." "Sure enough, the chauffeur gave a brilliant presentation and was doing well with the questions from the audience. That is, until a tax attorney asked a difficult question. There was a moment's pause as he reviewed the question. Then he loudly vituperated the poor man: "Sir, that's the dumbest question I've ever heard. It's so dumb that I'll bet you anything the chauffeur sitting in the back of the room can give you the answer." (As told by Thomas Cesario, VP from UC Irvine who lectured on "Update: antiviral therapy" at QMC Kamehameha Auditorium on April 9, 1993)

Conference Notes:

"Subclinical Hyperthyroidism" James Hennessey, Associate Professor of Medicine, Wright State University School of Medicine c/o Forest Pharmaceuticals

A. Introduction: This is the 102nd anniversary of the treatment of myxedema patients with sheep thyroid.

Historical use of thyroid:

(Continued) ►

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NEWS & NOTES (Continued from page 177)

a. obesity b. infertility c. fatigue d. hypercholesterolemia e. alopecia.

Accepted use of thyroid:

a. hypothyroidism b. nodule suppression c. goiter suppression d. postop suppression of benign and malignant lesions.

In 1986, 20 million prescriptions were written; today 24 million are being written. Prevalence of thyroid treatment: Framingham Cohort: 2/3 patients on desiccated between 1980 and 1984; 69%; 1988: 51%.

B. Thyroid Preparations:

a. Synthetics: eg Synthroid, Levothyroid b. Biologics: "Rational Mix" of T4 and T3 (preferred by nutritionists)

Reality: Biologic preps have no advantage over synthetic T4. T3 may even be harmful. With desiccated thyroid, T3 peaks while T4 remains steady. Side effects: cardiovascular and osteoporotic. Conclusion: Use synthetic preparations instead of biologics. Sodium Levthyroxine (Na T4): 1 week half life; T4 is converted to T3 in periphery. How much is enough? Replacement dose for the first 20 years: 0.2 to 0.4 Standardization: T3 better indicator of thyroid states in L-T4 treated patients TSH is best indicator of thyroid states.

C. Subclinical Hyperthyroidism:

Definition	T4	T3	TSH
1	High	High	Undetected
2	High	Normal	Undetected
3	Normal	Normal	Undetected
4	Normal	Normal	Detected

Symptoms:

a. Increased HR; b. Decreased day to night ratio of urinary Na excretion and urine flow; c. Short systolic time interval; d. Lower erythrocyte binding; e. Low CPK; Low serum creatinine; g. High sex hormone binding; h. decreased bone density. Long term L-Thyroxine Rx: osteoporosis; sub-

clinical hyperthyroidism a/c cardiac and skeletal abnormalities which may present clinical problems.

D. Recommendation for Hypothyroidism Therapy:

- Initiate 50 to 100 mcg daily.
- Goal: 1.7 mcg/Kg/d
- Keep HS-TSH within normal limits

E. Recommendations for Suppressive Therapy (Nodules or Ca)

- Initiate 50 to 125 mcg/d.
- Goal: 2mcg/Kg/d.
- Detectability: <HS-TSH <Nl.

TSH drops with age 2° lower metabolism and decreased renal function. Estrogen will not affect TSH values.

Conference Notes

(Visiting Professor Ronald A Arky lectured on "Hypoglycemic States: Some Molecular Biologic Aspects" on November 20 at Kamehameha Auditorium.

Introduction: Before Chronic Fatigue Syndrome, the diagnosis of hypoglycemia predominated. Always check carefully the drugs the patient is taking, especially the generics.

Regulation of Blood Glucose:

A. Fasting state:

a. Generator Liver b. Fuel: amino acids; lactate; glycol c. Regulator: enzyme; glycogenolysis; glycogenesis d. Modulator: 1. hormones; 2. insulin 3. cortisol 4. glucagon 5. growth hormone

B. Postprandial state: a. Generator: GI tract b. Fuel: glucose c. Regulator: Enzyme d. Modulator: 1. hormone 2. insulin 3. cortex regulators.

Cognitive Functions: Affected by hypoglycemia and drugs.

a. Cognition b. Neuropsychiatric c. Visual reac-

tion d. EEG changes.

*Higher centers require higher glucose levels.

*Hypoglycemia is the most common complication of IDDM.

Clandestine Severe Hypoglycemia: Nocturnal (Between midnight and 8 am); no varying while awake; symptoms not realized by patient.

Precursor Defects:

a. Ketotic hypoglycemia of infants b. adrenal insufficiency c. renal failure d. pregnancy — fasting, especially in the 3rd trimester.

Genetic Failure:

a. Hepatocellular disease, eg glycogen storage disease b. alcohol hypoglycemia.

Consumer Overexpenditure:

a. Insulin secreting tumors b. Extrapneumatic tumors c. Insulin excess states: Leucine sensitivity; infants of diabetic mothers; erythroblastosis fetalis.

Insulin secreting tumors: Incidence 1×10^6 per year; female/male ratio=2:1 Age: Under 40=20%; 40 to 60=40%; 60 and over=40%. Diagnosis: C-Peptide; fasting glucose; suppression test; tolbutamide test. Preop and intraop localization: ultra sound; arteriography; CT and MRIs.

Other hypoglycemic states:

a. Meostheliomas secreting insulin b. autoimmune hypoglycemia c. reactive hypoglycemia. Symptoms: Afternoon fatigue, depression, especially in women under 25. *Whipple's hypothesis: Fewer than 5% have hypoglycemia, ie the majority have something else.

Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol*. 1991;14:146-151.

PRAVACHOL® (Pravastatin Sodium Tablets) CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and Lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.** **Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (see DOSAGE AND ADMINISTRATION: Concomitant Therapy)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a \geq 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 30 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagenesis tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/– mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class

Skeletal myopathy, rhabdomyolysis

Neurological dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol, and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions).

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.



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Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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Highlights of the HMA Council Meeting of May 7, 1993

Members present were: J Chang, A Don, J Spangler, F Holschuh, S Wallach, R Stodd, L Howard, P Blanchette, C Lehman, R Lee-Ching, M Cheng, HKW Chinn, P Chinn, HH Chun, P Hellreich, R Kimura, M Shirasu, P Kim, J Betwee, H Percy, T Smith, G Goto, W Chang, A Kunitomo, J McDonnell, WWL Dang; F Reppun, Editor, *HMJ*; Legal counsel Vernon Woo; Auxiliary representative, S Foo; medical student M Rivera; HMA staff: J Won, N Jones, B Kendro, L Tong, J Asato, J Estioko, P Kawamoto and A Rogness, recording secretary.

President Jeanette Chang noted the great success of the HMA's Distinguished Medical Reporting Awards banquet on April 24, 1993, at the Ala Moana Hotel and its roast of Frank F. Fasi, Mayor of the City and County of Honolulu.

The State's HEALTH QUEST program, just announced and with permission for a waiver already on its way to the federal government, was fully discussed. QUEST is privatizing the Hawaii Medicaid program by having qualified insurers/providers bid for most of the Medicaid population and for the SHIP population as well, at a fixed capitation rate to be paid by the Hawaii State Government. It is to include comprehensive benefits. Because of many questions, issues and concerns, the HMA Council decided to take no position on this program until all information available to make such determination is known and disseminated to HMA members for their input.

The status of SHPDA and the CON process was raised. It was decided that the article written by Dr. Stodd for the

Maui News was an excellent analysis and should be published in the *Hawaii Medical Journal*.

President Jeanette Chang was invited by the AMA Speaker of the House, Daniel Johnson, to serve on the Committee for Rules and Credentials at the AMA Annual Meeting in Chicago this June.

The nomination of Dr. Brian Issell, Director of the Cancer Center of Hawaii, to again represent the University of Hawaii on the HMA Cancer Commission was approved by Council.

The CME Committee reported that, because of the impending merger of the CME program of the John A. Burns School of Medicine, University of Hawaii, with that of the HMA, the HMA/CME Committee will not be able to approve applications for co-sponsorship between October 17, 1993, and March 31, 1994. Anyone planning a CME program who needs assistance is urged to call the HMA/CME coordinator.

It was noted that Medicare now has a California-based Medicare fraud and abuse coordinator for the western states and Hawaii, and HMA will apprise the coordinator that the HMA stands ready to assist in any matters concerning Hawaii and its physicians.

Fred Holschuh
HMA Secretary



How about joining the HMA?

The big computer at the HMA offices has a list of all the physicians in the State of Hawaii; as of the month of March 1993 they number 3,013.

At the HMA Council meeting on 2 April this year, Secretary Fred Holschuh reported that our members number 1,808, of which 1,032 are "active, full paying". This means that less than 1/2 of the physicians in the State who are in the active practice of medicine have joined in order to support an organization that works for the benefit of all physicians. The others are deriving the benefits—such as they are—without contributing to the effort. That is a shame.

The Hawaii Bar Association, in contrast, mandates membership as a requirement of the license to practice law.

Just think! If the other 1,150 or so practicing physicians become members of the HMA through their county medical societies and put their shoulders to the wheel, our dues could be reduced by at least a half if not more!

What more—a great deal more—is that HMA's impact on the future practice of medicine that is, of course, for the benefit of our patients, would carry a great deal more weight

at the State Legislature as well as at the federal level.

As is true of so many eleemosynary organizations, the few labor for the benefit of the many, and that is a shame.

In an attempt to encourage more young physicians who are just starting to practice medicine to join us at the HMA, the Council has authorized billing only 20% of the regular dues the first year, and 20% more each year the next 4 years until full dues-paying membership is reached in the 5th year. This is based on the impression that it is the amount of the dues that is the major drawback to joining (the latter bit of reasoning is somewhat incredible because societal dues are a part of a physician's overhead expenses, therefore, fully deductible).

We invite the 1,148 nonmembers to join the 1,032 of us who are members, to join in the work that benefits us all, and to share in paying for such, thus making it easier for us all who strive to improve the care of our patients.

The editor

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Intraoperative Transesophageal Echocardiography

RC Ashmore MD*

MT Grattan MD*

JR Chen MD*

WJ Kai MD*

CE Moreno-Cabral MD*

NM Scully MD*

EN Shen MD*

RL White MD*

Intraoperative echocardiography in patients undergoing cardiac surgery was first described in 1972¹. Interest in intraoperative echocardiography has grown in recent years due to the extensive information provided by 2-dimensional (2-D) and color-flow Doppler imaging via the transesophageal approach². The value of this technique also has been verified in large clinical studies involving patients undergoing cardiac surgery^{3,4}. Intraoperative transesophageal echocardiography (TEE) is very useful in preoperative formulation of surgical plans and in immediate postoperative assessment of surgical results in patients undergoing valve surgery.

Introduction

This technique has proven to be valuable in assisting in the management of patients undergoing coronary artery bypass graft surgery (CABG) complicated by the presence of ischemic mitral regurgitation (MR)⁴. Significant MR is present in up to 20% of patients with coronary artery disease, and patient survival post-CABG directly correlates with the severity of the residual postoperative MR⁵. Although this may suggest an aggressive approach to ischemic MR during CABG with mitral valve repair/replacement, performing such a combined CABG and mitral valve procedure significantly increases operative mortality⁶. Therefore, the careful selection of patients subjected to combined procedures is imperative. Intraoperative TEE can provide accurate and timely information to guide the surgical approach to therapy of ischemic MR during CABG.

This technique has been used at Straub Clinic & Hospital since May 1991. In our manuscript we describe a case series of our initial experience in 31 patients undergoing intraoperative TEE to assist cardiac surgery. Although patient numbers are small, our early experience with this technique supports its usefulness in selected cardiac surgery patients.

Methods

Patients: Thirty-one patients undergoing cardiac surgery with intraoperative TEE between May 1991 and July 1992 were studied. Fourteen patients underwent surgery for primary

valvular disease (12 mitral valve disease and 2 aortic valve disease with associated MR), 14 patients underwent CABG complicated with ischemic MR, and 3 patients underwent cardiac surgery for other indications (one acute Type I aortic dissection, one aortic valve endocarditis with sinus of valsalva fistula, and one atrial myxoma).

Intraoperative TEE: Two-dimensional and colorflow Doppler echocardiograms were obtained using a Hewlett-Packard 77020AC imaging unit and a 5.0 MHz single plane, esophageal-probe transducer. The probe was placed after general anesthesia induction and endotracheal intubation. Initial images were obtained prior to cardiopulmonary bypass (post-bypass) and followup images were obtained postcardiopulmonary bypass (post-bypass) prior to surgical closure. An effort to increase both preload and afterload through volume expansion was made when necessary to provide comparable loading conditions for pre- and post-bypass TEE. Standard 2-D views with colorflow Doppler imaging were obtained pre- and postoperatively and stored on high-fidelity videotape for later review.

Intraoperative Tee Interpretation: The pre- and post-bypass 2-D and colorflow images were all interpreted during the surgical procedure by a cardiologist and by a thoracic surgeon. All operative decisions then were made on line. Videotapes of all patients studied were reviewed off line for the final interpretation and the results are listed below. The severity of MR was graded 1+ to 4+ as previously described⁴.

Cardiac Catheterization Interpretation: Preoperative cardiac catheterization was performed 3 to 93 days (mean 25.7 days) before surgery in patients with primary valvular disease and 0 to 34 days (mean 11.4 days) before surgery in patients with CABG complicated with ischemic MR. The severity of MR was assessed from single plane ventriculography by consensus agreement of 2 cardiologists on a 0 to 4+ scale as previously described⁷.

Results

Primary Valvular Disease Surgery: The post-bypass TEE was utilized by the thoracic surgeon in 14 primary valvular disease operations. The information provided by post-bypass included the severity of MR and the amenability of the mitral valve for surgical repair. The severity of MR by preoperative angiography and post-bypass TEE are shown in Table 1. MR measured by post-bypass TEE showed excellent correlation

(Continued on page 188) ►

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with preoperative angiography in patients with primary valvular disease (none of 14 patients had significant discordance, ie $> 1+$ difference between post-bypass TEE and preoperative angiography).

Decisions regarding mitral valve repair versus replacement were made intraoperatively utilizing post-bypass TEE data and intraoperative valvular inspection. Five of 12 patients with primary mitral valve disease and 1 of 2 patients with primary aortic valve disease and concomitant MR successfully underwent mitral valve repair. All patients undergoing mitral valve repair had technically satisfactory results as judged by the surgeon and post-bypass TEE.

CABG with ischemic MR: Fourteen patients undergoing CABG with ischemic MR had intraoperative TEEs performed. The results of MR severity measured by preoperative angiography and by post-bypass TEE are shown in Table 2. The post-bypass TEE exhibited significant discordance ($> 1+$ difference) from preoperative angiography in 6 of 14 patients. Two of these 6 patients underwent combined CABG with mitral valve surgery.

These patients all consented to CABG with or without mitral valve repair/replacement. The decision to perform mitral valve surgery was made using post-bypass TEE data and intraoperative valvular inspection. Five of the 14 patients underwent concomitant CABG with mitral valve repair or replacement. One patient initially underwent CABG without mitral valve surgery. Post-bypass TEE data in this patient revealed 3+ MR and the surgeon then elected, after bypass, to perform a mitral valve repair.

There were no complications associated with the intraoperative TEE in any of the 31 patients.

Discussion

Interest in intraoperative echocardiography has greatly increased recently due to the growing numbers of complex surgical procedures being performed and to the usefulness provided by intraoperative TEE. Our series describes the value of this technique in assisting the management of selected cardiac surgery patients. Intraoperative TEE was of the greatest value in assessing patients undergoing possible mitral valve repair and patients undergoing CABG complicated with ischemic MR. The technique provided valuable information in formulating the surgical plan, in assessing immediately the operative results, and in identifying patients at risk for postoperative complications.

Mitral valve repair is proving to be a viable alternative to valve replacement in selected patients with MR⁸. By understanding the mechanism of MR and by assessing the valvular and subvalvular apparatus, the surgeon can successfully undertake valve repair in many patients. Post-bypass TEE can provide essential information to aid in surgical planning by assessing the feasibility of valve repair. Post-bypass TEE is of equal importance. First, post-bypass TEE is superior to previous methods in assessing residual MR⁹. This is extremely important since the degree of residual MR directly correlates with postoperative mortality⁸. Second, other postoperative complications following mitral valve repair, such as left ventricular outflow obstruction and left ventricular dysfunction,

are readily identified by post-bypass TEE. The timely recognition of postoperative complications should allow for prompt measures in corrective management; this should improve surgical results.

The use of intraoperative TEE in patients undergoing CABG with ischemic MR has recently been described⁴. MR occurs in up to 20% of patients with coronary artery disease and in up to 50% of patients with acute myocardial infarction. The MR that has not been corrected, after CABG, is an independent predictor of long-term survival⁵. Since operative mortality increases with combined CABG and mitral valve surgery, careful selection of patients for a combined procedure is imperative. Sheikh et al⁴ showed that post-bypass TEE resulted in a change in the operative plan in 11% of patients undergoing CABG with ischemic MR. Therefore, the assessment of MR severity at the time of surgery is helpful in planning the operative procedure. At our hospital, patients are routinely asked to consent to CABG with or without mitral valve replacement/repair, thereby relying on the post-bypass TEE data for management decisions.

In our series, 6 of 14 patients exhibited significant discordance between preoperative angiography and prebypass TEE. This discordance was not seen in the patients with primarily valvular disease. Our experience is similar to larger studies documenting discordance measured by angiography and TEE in patients with ischemic MR⁴.

Although the cause of the discordance seen in ischemic MR is unclear, multiple explanations have been suggested. First, the severity of ischemic MR can be very labile depending on the degree of ischemia at the time of measurement. Second, although attempts were made to measure MR at comparable preload and afterload parameters, differences in loading conditions may have contributed to the discordance seen. Finally, although previous studies comparing Doppler techniques to cardiac catheterization in MR measurement have reported good correlations¹⁰, differences in the 2 techniques also could have affected the results.

Intraoperative TEE can provide valuable information in other selected cardiac surgery patients, such as in the repair of aortic dissection and in the repair of congenital heart disease. Additionally, postbypass TEE is helpful in detecting postoperative left ventricular dysfunction and residual intracardiac air, allowing for implementation of immediate corrective measures.

In our series, we have shown the value of intraoperative TEE in the management of selected cardiac surgery patients. These data support previous larger clinical trials^{3,4}. The technique provides timely information with minimal risk to the patient and is performed without interruption of the operative procedure or the intrusion of equipment into the operative field.

Intraoperative TEE should be considered in all cases of possible mitral valve repair and in all cases of CABG with significant ischemic MR.

ACKNOWLEDGEMENTS

The authors would like to gratefully acknowledge Irene Yamachika LPN for her assistance in data correlation and Cathy L. Ow MD for her critical review of the manuscript.

(Continued on page 201) ►

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Primary Caffeine Dependence: A Case Report

Douglas Adams MD, Capt MC*

Thomas Ditzler PhD**

William F Haning MD, Cmdr, USN, MC***

We present a case of primary caffeine dependence based on the exclusive use of over-the-counter caffeine tablets. Caffeine has recently undergone scrutiny as a co-morbid risk factor with other substance dependencies, and in other medical and psychiatric conditions. Caffeine withdrawal also is briefly discussed with attention given to personality factors and the use of nicotine. Although caffeine generally is considered safe in usual doses, it is a substance potentially able to result in serious dependence. We cite a case which also illustrates that a supportive inpatient milieu may be necessary in order to interrupt a cycle of heavy caffeine use resulting in marked dependence.

Introduction

Despite its ubiquitous use^{1,2,3} and acceptance as a relatively safe drug, caffeine has recently come under scrutiny as a potent pharmacologic agent that exerts significant effects on a number of organ systems. Investigators have examined the possible adverse role of caffeine in affecting hypertension, coronary artery disease, hyperlipidemia, irritable bowel syndrome, peptic ulcer and pancreatic cancer^{3,4}. Psychiatric literature has reported that caffeine has exacerbated panic disorder⁵, anxiety^{6,3}, depression⁶, schizophrenia⁷ and insomnia^{1,3,6}. In addition, caffeine has received recent interest as a risk factor for relapse among patients suffering from alcohol or nicotine dependence⁸.

Epidemiologic evidence suggests that the average intake of caffeine by adult Americans is approximately 200 mg to 220 mg a day^{1,3}, and that intake in excess of 788 mg a day probably occurs in only 0.1% of the population¹, which would correspond to the intake of approximately 9 cups of brewed coffee. Our report describes primary caffeine dependence in an otherwise healthy man and illustrates that caffeine itself, regardless of co-existing medical or psychiatric conditions, has the potential to act as a drug that can be abused with serious consequences.

Case Report

The patient was a married 29-year-old man who was referred to the Psychiatric Inpatient Service of Tripler Army Medical Center (TAMC) for treatment of primary caffeine dependence. The medical history revealed in addition a consumption of 40 to 60 cigarettes a day for 11 years, but other-

wise, the patient had no significant medical or psychiatric problems or history of alcohol or illicit drug abuse. The patient began the use of over-the-counter caffeine tablets approximately 10 years prior to admission. He began taking one or two 100 mg tablets at night to help him remain alert while moonlighting at a second job. The patient's primary job as a radio operator required protracted attention to detail in an often lengthy procession of incoming traffic messages, which then required prioritization and dissemination. Shifts lasting from 8 to 15 hours heightened the appeal of caffeine's stimulating effect. As tolerance developed, the patient increased his dosage pattern to 3 or more times a day for a total daily consumption of 1600 to 2000 mg. A typical regimen consisted of two 200 mg caffeine tablets 4 times a day. The patient's longest period of abstinence was 6 months, after he was moved from shore duty onto a ship where caffeine tablets were not available. Interestingly, he denied the use of caffeine-containing beverages. When asked why he sought help to stop his use of caffeine, he cited a chief complaint of recurrent withdrawal headaches (which he medicated with 1 to 2 caffeine tablets), as well as chronic irritability and an increasing concern for his long-term health.

Because he had demonstrated the inability to stop the use of caffeine on his own, he was admitted to Inpatient Psychiatry in order to provide environmental and pharmacologic support in case of serious caffeine withdrawal symptoms.

On day 1, he denied headache but complained of generalized anxiety and a sense of feeling trapped. On day 2, he complained of a dull, bifrontal headache of an intensity 5/10 associated with nasal fullness (this responded to Motrin and Actifed), as well as generalized fatigue. On day 3 his headache was significantly reduced to 1 to 2/10. His daytime sleep reduced from 4 hours to approximately 1 hour. On day 4, he began to experience an increased subjective sense of energy and well-being and no longer asked for medication for headache. On day 5, he again experienced significant daytime somnolence requiring several naps. Day 6 was essentially without physical complaint, and he was discharged on day 7.

At no time did he complain of cardiac symptoms, muscle tension, tremulousness, nausea or dyspepsia. Although irritable at times, his affect was appropriate in the milieu of the ward and he was a highly verbal participant in group sessions.

Discussion

Primary caffeine-dependence is rare. Pathologic consumption of caffeine is most often associated with an attempt to manage intentional or inadvertent withdrawal from amphetamine or other sympathomimetic drugs. This patient's

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consumption of caffeine in tablet form, coupled with his distaste for caffeine-containing foods and beverages, reinforces the notion that the consumption is for the sole purpose of achieving an altered state (psychotropic effect).

Our patient clearly met the diagnostic criteria for psychoactive substance-use disorder. Over time he had consumed caffeine in even larger amounts, more than he had intended, and his history revealed unsuccessful attempts to control this abuse. He had achieved marked tolerance. He had experienced an abstinence syndrome and he had taken caffeine to relieve or avoid these withdrawal symptoms. He had continued its use despite the presence of negative consequences and he was concerned about his long-term health.

The patient's withdrawal symptoms were uncharacteristically mild; his response to Motrin and Actifed was unexpected but gratifying. Caffeine-withdrawal headache is classically reported to be of a severe, generalized, vascular type accompanied by photophobia and nausea in 25% of sufferers.^{2,6} Traditional treatment regimens are those used in cases of severe migraine. A partial explanation for this patient's relatively mild withdrawal is not unusual considering the wide range of individual differences in both tolerance and withdrawal from methylxanthines. Personality factors including extroversion, tendency to avoid somatization, and self-assessment of overall good health (this patient displayed all) have been associated with the ability to tolerate and enjoy the effects of high doses of caffeine^{1,2}.

These personality traits also have been associated with a decreased intensity of withdrawal headaches. A significant factor could be that the patient smoked cigarettes, since nicotine has been shown to decrease significantly the plasma half-life of caffeine by as much as 50%.^{6,9} In addition, the patient's reported withdrawal symptoms during previous attempts to discontinue caffeine were apparently much worse than the withdrawal he reported while he was hospitalized. This suggests that the additional psychological factors were operating within the inpatient milieu. Thus, removing the patient from his regular daily stressors, providing pharmaco-

(Continued on page 194) ►

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Testicular Microlithiasis: Ultra Sound Appearance

Joseph A Gagliardi MD*

Kristen A Freestone MD*

Dean J Shanley DO*

Testicular microlithiasis is a diffuse, benign condition involving both testicles without architectural distortion. Multiple, bright echoes are present on ultrasound examination which rarely cause shadowing. Many associated conditions have been reported in patients with this entity. As this is a benign entity, knowledge of its appearance and associated conditions to prevent unnecessary surgery is important.

Introduction

The testicles are excellent transmitters of ultrasound waves and are easily evaluated by using 7.5 MHz or 10 MHz transducers. The echogenicity of the testicles is composed of homogeneous medium-level echoes quite similar to those seen in the thyroid gland. Frequently a linear area of high signal is seen posteriorly representing the mediastinum testis. The mediastinum testis is composed of thickened connective tissue containing the arteries and veins supplying the testis and blends in with the tunica vaginalis.

The normal testicle is elliptical in shape, measures approximately 3.5cm in length and 3cm in diameter. Evaluation of both size and shape of each testicle as well as internal echo characteristics is paramount in diagnosing pathology.

Calcification within the testicle is usually a sign of neoplasm, trauma, infection or a vascular abnormality. A rare entity, testicular microlithiasis also may cause diffuse calcifications in the testes.

A study by Vegni-Talluri et al evaluated testicular microlithiasis by both light and electron microscopy and concluded that these tiny calcifications represented degenerating intratubular cells in the seminiferous tubules¹. The calcifications were surrounded by a laminated shell composed of cytoplasmic debris and collagen fibers.

Patients with testicular microlithiasis can be completely asymptomatic and have no prior history of trauma, infection or vascular insult². Studies have shown an association between testicular microlithiasis and cryptorchidism³, with Klinefelter's syndrome⁴, male pseudohermaphroditism⁵, neoplasm¹, and in a patient with both pulmonary alveolar microlithiasis and sympathetic nervous system calcification⁶.

Interestingly, both patients had associated hydroceles, an association that previously has not been reported with testicular microlithiasis.

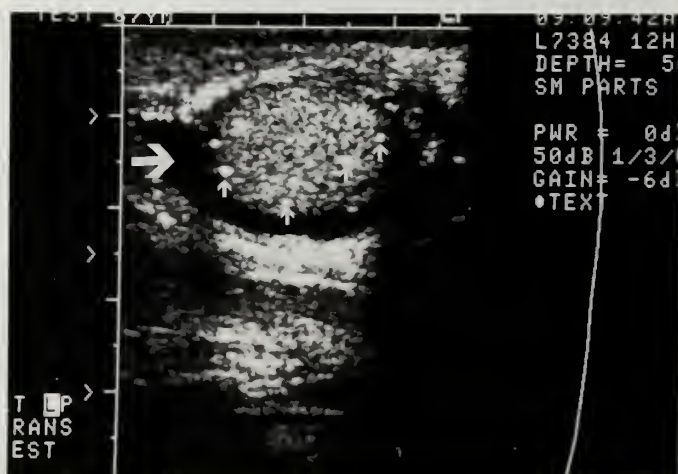
Figures 1 and 2 are of a patient who was noted to have a

swollen testicle during a physical examination. Ultrasound revealed small peritesticular fluid collection consistent with a hydrocele, together with multiple small punctate hyper-echoic lesions diffusely present throughout the testicle. There was no distortion to the testicular parenchyma in this patient; his past medical history was noncontributory. Acoustic shadowing was absent and the process was bilateral.

The other patient presented with an enlarging left testicle with chronic dull aching pain. There were no clinical or lab-



Figures 1&2: Longitudinal and transverse scans demonstrate a homogeneous left testicle with multiple, small, bright internal foci without acoustic shadowing (small white arrows). The surrounding anechoic fluid collection seen in both projections represents a hydrocele (large white arrows). No overlying skin thickening is noted.



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oratory findings suggestive of infection; a history of trauma also was absent.

Ultrasound revealed large anechoic peritesticular fluid collection (Figs 3 & 4), along with multiple nonshadowing punctate echodensities spread diffusely throughout the left testicle. In addition, an abnormal inhomogeneous echotexture was noticed. Scanning through the right testicle demonstrated diffuse echogenic foci without architectural distortion or homogeneous echotexture.

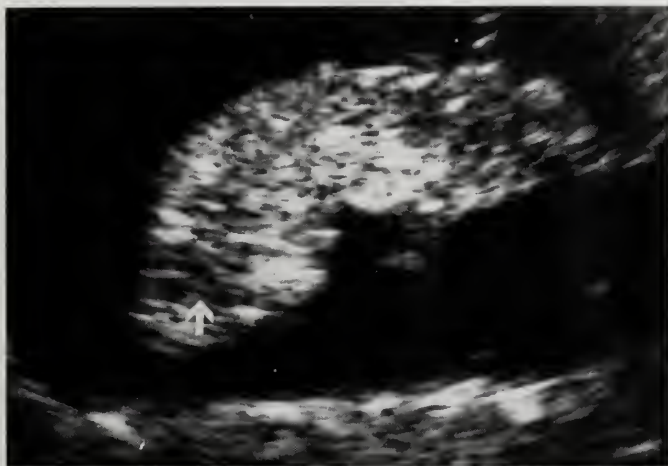
At resection a large left hydrocele was present along with testicular microlithiasis and a lobulated embryonal-cell carcinoma.

Mammographic examination of the resected testicle revealed multiple punctate calcifications with an appearance similar to degenerative breast disease or sclerosing adenosis (Fig. 5).

Testicular microlithiasis usually presents as multiple, tiny, bright echoes, usually without acoustic shadowing. There should be no apparent distortion of the parenchyma; however, the microlithiasic specks may be so numerous that attenua-

tion of the sound beam may limit evaluation of the deep structures within the testicle. Normal testicles on ultrasound are homogeneous and any abnormality requires an explanation. Most of the abnormalities clinicians look for are neoplastic, and thus surgery follows. If tiny, punctuate, bright echoes are diffusely present without any architectural distortion; the diagnosis of testicular microlithiasis is made. If unsure a follow-up scan in 4 to 6 months can be obtained to assure stability but surgery is not indicated just for microlithiasis.

The statement "surgical intervention is not needed" is an important take-home message regarding this entity. As more and more clinicians are performing sonography in their offices, this diagnosis is an important one.



Figures 3&4: Two longitudinal views of the left testicle demonstrate an inhomogeneous internal architecture (arrows) that represent the patient's embryonal cell carcinoma as well as multiple punctuate bright foci without acoustic shadowing secondary to microlithiasis. The black region surrounding the testicle represents the patient's large hydrocele.



Figure 5: Mammographic evaluation of the bivalved left testicle, figures 3 and 4, demonstrates multiple punctate radiodensities consistent with microlithiasis.

ACKNOWLEDGEMENT:

The authors are grateful for Ms. Karen H. Akagi's preparation of the manuscript.

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PRIMARY CAFFEINE DEPENDENCE: A CASE REPORT

(Continued from page 191)

logic support of his withdrawal symptoms and providing an aura of safety in the ward may have been instrumental in interrupting the cycle of compulsive abuse in this case.

In cases involving heavy compulsive caffeine use such as this, brief inpatient hospitalization deserves consideration.

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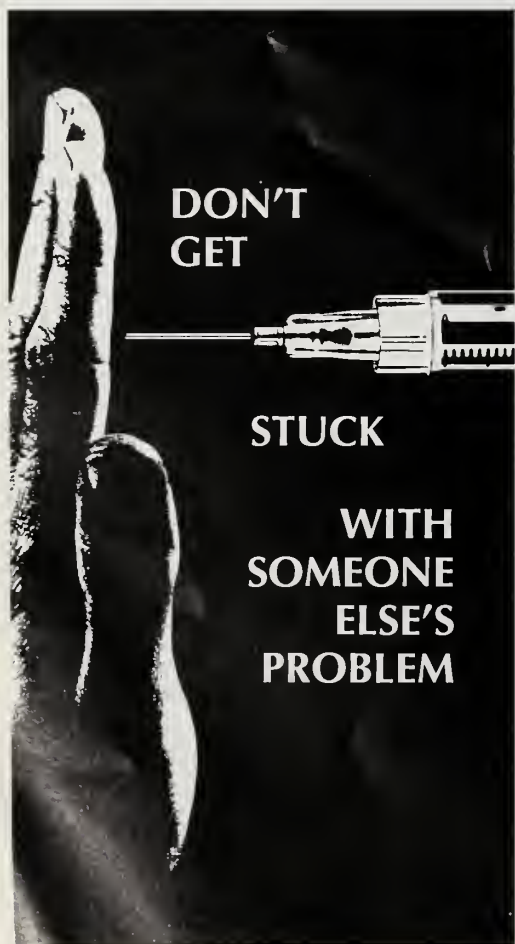
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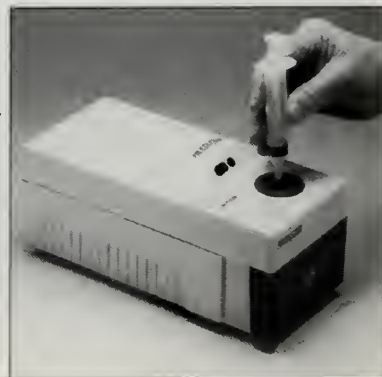
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Dedication of the Robert J Emrick MD Library

On March 9, 1993 we dedicated GN Wilcox Memorial Hospital's new medical library to Robert Emrick, our pathologist from 1964 to 1988. Since many HMA doctors knew Dr. Emrick, we thought you might be interested in the remarks made on that occasion.

It was very gratifying to see so many of you here. Sophie Cluff admonished me to make my remarks "short and snappy"! I tried to comply, however, in deference to those who came from Oahu and the Mainland, I will risk incurring her censure.

Bob Emrick was a great colleague, friend or family member to many of us. He was a founding father of Kauai Medical Group (KMG) and was always a staunch supporter of Wilcox Hospital. He realized that our strengths are multiplied by cooperation and greatly diminished by the unpleasant turf battles which to some extent have marred the years since his passing. These would have disturbed him greatly. It is propitious that we should be dedicating this library today because the tide has changed and it seems that "The Medical Group" and "The Hospital" are on the path of cooperation that will serve Kauai's people first, and not any special interest group primarily.

Bob died on October 4, 1988. In the 4 1/2 years since his death, it is amazing how many new faces there are on our staff. More than half of the doctors today and many other hospital and KMG workers either did not know him well or never even met him. Some have never even heard his name.

In 1909, Sir William Osler said on the occasion of dedicating a hall to him at the Maryland Medical and Chirurgical Johns Hopkins, "These [events] illustrate how quickly the memory of a name perishes. In how many minds did the mention of David Hosack arouse a thrill of remembrance? His works—and they were good ones—have perished, and his more enduring association is with the hall which bears his name. We can imagine a conversation in the library—AD 2009—between 2 assistants wearily sorting a pile of second-hand books just in. "What are we to do with all this rubbish by a man named Osler? He must have had very little to do to spoil so much paper. Where did he live anyway?" "Oh I don't know, Baltimore I think. Anyway, they have a hall there that bears his name." This holds equally as well for Bob Emrick whom we honor today.

I suggest that some of you gathered here—colleagues, friends, family—submit short remembrances of Madeleine and Bob Emrick which we can bind and store in the library, so that those curious members of our medical community in years to come can learn just what kind of people the Emricks were. Perhaps we may not see their likes again.

Bob Emrick was a child of the coal mines of Ohio. Born to a family of modest means, he did not have the financial resources to enter medicine right away. He was fond of telling friends about his first job while still in high school—working for a bookie in small towns of southeastern Ohio. Later he was a court stenographer. He met his wife Madeleine in Ohio where she was studying art at Ohio State University. Madeleine, who grew up in Lebanon Springs, New York, must have been a free spirit in her own right because she

left the Berkshire mountains before WWII to spend some years in Honolulu. After the war, her humanitarian convictions led her to leave Hawaii to volunteer for work with Quakers caring for displaced persons in France and Spain.

After they married, Bob went to Ohio State University Medical School in 1957. Upon graduating, since Madeleine had told him so much about Hawaii, they returned to The Queen's Hospital for his internship. The next year, Bob worked in rural Hawaii—mostly at Laupahoehoe on the Big Island. The Emricks then moved to Boston where Bob did a pathology residency at the Mallory Institute; after completing this, he moved to Kauai in 1964 to be our first full-time pathologist.

When I came to Kauai to interview for my first real job as a physician, Bob Emrick was one of the initial people I met. We developed a fast friendship. Many was the hour we spent in his office discussing medicine and life in the old cafeteria and in our Kalaheo homes. To me, he was always kind and generous; but there were those he didn't tolerate. Few, if any of them, ever gained his affection. In the 14 years that I knew him, I never saw him put his or his family's interests above those of our community or hospital—neither in desire for income nor in property or prestige. I think that he feuded with those he perceived had a *me-first* approach to life.

Lewis Landsberg, in a recent article on altruism in medicine, writes: "[Doctors], by our behavior, have contributed to public disaffection with medicine. We have squandered what was once our most precious asset: the overwhelming trust and gratification of the people we serve. What has happened to alienate the public? We are perceived as self-interested businessmen rather than as dedicated physicians or scientists. We have contributed to the commercialization of medicine, a commercialization that I believe is at the root of many of our problems."²

Bob Emrick would have agreed with this. Bob didn't cotton to businessmen-physicians. I can say this comfortably here, because the businessmen-doctors wouldn't bother to come here today. They weren't Bob's friends.

It is fitting that we dedicate this room to one who was very committed to this institution. It affirms what he stood for, since the library is a crossroads where all of our staff will gather for inspiration and enlightenment.

Some who are here may not know how generous Madeleine and Bob were to the Wilcox Hospital Foundation. Indeed, Bob was one of its founding members. The Emricks donated substantial sums to our Foundation, and after Bob's death, Madeleine stipulated that a portion of their bequest be earmarked toward establishing this library. Since they had no children to carry on their kind works on Kauai, in this way the Emrick name will not be threatened with extinction on this speck of firmament they loved so much.

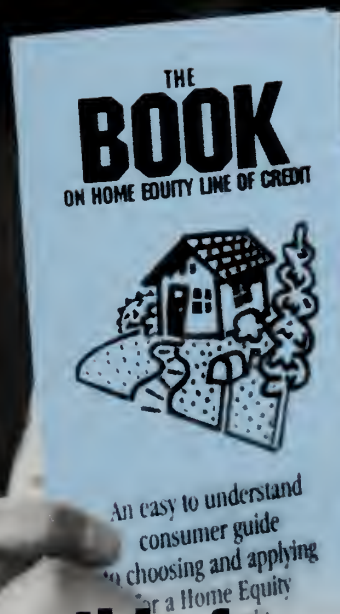
Sadly for those who knew her, Madeleine developed cancer a little over a year after Bob died. She succumbed in September, 1990. I, who knew her well, felt that she had no desire to live without her beloved Bobbie, her companion at Honua Farm. To the many people who knew and loved her, this Library is a tribute to Madeleine Chevalier Emrick as well as to Bob.

(Continued on page 198) ►

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DEDICATION OF THE ROBERT J EMRICK MD LIBRARY ON KAUAI

(Continued from page 196)

A Chinese sage said: "To die but not to perish is to be eternally present." This room will carry the spirit of the Emricks in it and will maintain their presence for those of us who use it.

The Robert J Emrick Library makes me proud of our institution. This library was slow in coming, taking more than 4 years since Bob's death to materialize. There were revisions, new wings, ICU renovations, changes in Wilcox's administration—and Hurricane Iniki.

That the library is here at all has as much to do with the quiet perseverance of Sylvia Duarte, our medical staff services factotum, who followed the idea from its inception through the many snags and roadblocks we experienced. I'm sure that if Sylvia were not here the idea might have foundered. Sylvia was one of those whom Bob Emrick held in high esteem (although she probably did not know it).

Sometimes as we pay so much attention to acquiring *state-of-the-art* technology, I fear we may lose sight of the importance of an excellent hospital library. While equipment is phased out rather quickly to make room for newer, more expensive and sometimes better technology, we have not always kept pace with our storehouse of knowledge—our library.

For the past few months, I have been immersing myself in the life of Sir William Osler—America's preeminent physician—whose name may not be as familiar today as it was 50 years ago. Osler was a great bibliophile and believed that the medical library was the cornerstone of medical practice. Indeed, he was a curator of the renowned Bodley Medical Library at England's Oxford University.

William Osler wrote: "To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all...for the general practitioner a well-used library is one of the few correctives of the premature senility which is so apt to overtake him. Self-taught, he leads a solitary life, and unless his everyday experience is controlled by careful reading, or by the attrition of a medical society, it soon ceases to be of the slightest value and becomes a mere accretion of isolated facts without correlation. It is astonishing with how little reading a doctor can practice medicine, but it is not astonishing how badly he may do it."

He goes on: "Books are tools; doctors are craftsmen, and so truly as one can measure the development of any particular handicraft by the variety and complexity of its tools, so have we no better means of judging the intelligence of a professional than by its general collection of books. A physician who does not use books and journals, who does not need a library, who does not read one or two of the best weeklies and monthlies, soon sinks to the level of the cross-counter prescriber; and not alone in practice, but in those mercenary feelings and habits which characterize a trade."

Osler also seems to speak to us in a letter he wrote in 1908 to the physicians in Vancouver, British Columbia, on the occasion of their organizing a medical society. "I am very glad to hear that you have started a library. There is no better index of the intellectual status of the profession in any town than the condition of its medical library. It will do you all so much good to work at it, particularly in connection with the medical society. Let me indicate briefly the lines along which you should develop:

1) The current journals, general and special, taking particularly those not likely to be subscribed for by the individual members;

2) as soon as possible fill up one or two sets of first-class journals: the *Lancet*, the *BMJ*, the *American Journal of Medical Sciences*, the *Annals of Surgery* and the journals of that type;

3) of the books, get the good systems and special works in each department rather than ordinary school texts...I hope that every physician in the place will feel that he or she should help as much as he or she possibly can, not only by his or her individual subscription, but, when he or she feels he or she can afford it, by an occasional donation. Tell some of the members from me, please, that money invested in a library gives much better returns than mining stock."

On October 17, 1929, shortly before the great stock market crash, Henry Cushing, another great founding father of modern American medicine and Osler's biographer, spoke at the blessing of the William Welch Medical Library at the Johns Hopkins School of Medicine. He said: "The dedication of a library is usually a commonplace event which calls for certain platitudes, perhaps even a prayer. The generosity of the donor is praised, the genius of the architect; the educational needs of the people (other than those present) are recalled, and assurance given that they will be met so far as a meager endowment permits. [Finally] with some relief all adjourn for lunch."

Harvey Cushing had obviously been to more of these affairs than I have. I'm sure that Madeleine and Bob would appreciate his words and smile wryly at how similar this event is to others. Like Sophie Cluff, they would have said: "Dave, for God's sake get this over with!"

They also would have appreciated what Cushing said about making the library accessible to *all interested health providers*—nurses, doctors, therapists.

At the present time, there is a rule that says that only Wilcox doctors and staff can use the library. Knowing the Emricks as I did, I think this would have upset them. I turn again to Cushing who wrote: "Given a good working library rich in its books of reference, its usefulness depends on the *encouragement and convenience it offers to the reader*, no less than on the infectious enthusiasm of its working staff. A library unexercised, and which takes no chances in life, is susceptible to the deterioration and sclerosis certain to attend a poor circulation. [Therefore] a library must make unselfish use of its possessions even at the risk of an occasional loss."

I reread a section of the *Tao Te Ching* a few days ago that reminded me of Madeleine and Bob. I have copied it for those who are interested. The Emricks were the type of people whom the Chinese sage Lao Tse was speaking about 2,500 years ago when he wrote⁸:

He who knows men is clever;
He who knows himself has insight.
He who conquers men has force;
He who conquers himself is
truly strong.

He who knows when he has enough
is rich,

(Continued) ➤

And he who adheres to the path of
Tao is a man of steady purpose.
He who stays where he has found
his true home endures long,
And he who dies but does not perish
is forever present.

David J Elpern MD
Kauai

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Injustice is easy to bear. What stings is justice.

An experienced California eye surgeon was found negligent in both his radial keratotomy surgery and in misrepresentation of the procedure. The patient, a 42-year-old contractor, was promptly changed from a 5-diopter myope to a 3-diopter hyperope on one eye, and the surgeon assured him that he would improve. Surgery was performed on the second eye six weeks later with a similar result. The plaintiff claimed that, when he was presented with the consent form, the doctor stated it was only a hospital formality and he need not bother to read it. At the time his eyes were dilated, so he elected to sign the informed consent sheet without reading it. One year post-RK, consultation with a corneal specialist revealed that the patient had +8 to +12 diopters of hyperopia, could not wear contact lenses, and needed 12 pairs of glasses to deal with his fluctuating vision. He could no longer work as a contractor, had lost his business and had to sell various properties in order to maintain his family. The jury arrived at a verdict of negligence, but not fraud, and awarded \$5.4 million to the plaintiff. The MICRA limit of \$250,000 on noneconomic damages reduced the total loss to just over \$3 million.

The course of progress — most things get steadily worse.

Despite promises and carefully crafted legislation, some politicians now want to open the physicians data bank. Congressman Ron Wyden of Oregon has now put on his other face. "To make the market system work, you need public access to the kind of information in the data bank." However, one of Wyden's basic premises in supporting the NPDB law was that confidentiality would be maintained and that access to information would be fastidiously limited to those who need to know, ie hospitals, state medical boards, licensing agencies, HMOs, et al. The AMA hierarchy is fuming and every practicing physician should be enraged! AMA Executive Vice-President James Todd MD has stated

the only people agitating for this are "people who have a generic dislike of physicians." Term limits, anyone?

To insure peace of mind, ignore rules and regulations.

If I rent your oven and bring my own dough, should you keep the bread if you bake it? In California, the state Supreme Court ruled that a surrogate mother who contracted to carry a test-tube baby was not allowed to keep the offspring. No genetic link, then no baby. Wisely 18 states have laws prohibiting or restricting commercial incubation of human births. In another legal decision, a judge in Michigan struck down a state law prohibiting doctors from helping terminally ill patients commit suicide. The statute was directly aimed at Jack Kervorkian MD who has assisted in 18 suicides since 1990. Dr. Kervorkian appears to take perverse pleasure in being outside the envelope.

The "conspiracy of silence" has been replaced by a stampede of avarice.

In California, a patient filed a lawsuit for loss of hearing and equilibrium after TMJ surgery. Because such nerve damage is a known complication of the procedure, no oral surgeon or otolaryngologist would testify for the plaintiff. The attorney for the patient found a doctor who had retired 10 years earlier and had never performed the operation to state that the surgeon was negligent. The jury believed the plaintiff's expert witness and awarded \$400,000 in damages. The California Medical Association wants to present an *amicus curiae* on behalf of the defendant on his appeal and also hopes that the definition of who can testify as an expert will be less liberal. With this case informed consent becomes meaningless.

All American cars are basically Chevrolets.

Shopping for a new car? The AAA says that if you plan to spend less than \$25,000, buy American. Best picks are (scaling up): Ford Escort, Geo Prizm, Dodge Intrepid and Olds 88. Above

\$25,000 the strata are: Saab 9000, Lexus SC300, BMW 525i, Cadillac STS, Lexus LS400, and Mercedes Benz 400SEL (over \$50,000). (Ralph Nader says the price is higher if you are female.)

To find the submerged politician follow the oil slick.

Did you ever wonder which Congresspersons received the greatest political contributions from health-industry PACs and contributors in the 1992 election campaigns? Right here in the *Weatherlane* are the top ten recipient lawmakers and their health care spending money (a drum roll): Senators Packwood (R-Ore) \$186,400, Daschle (D-SD) \$173,500, McCain (R-Ariz) \$158,383, Grassley (R-Iowa) \$142,490, Coats (R-Ind) \$124,050, Specter (R-Pa) \$109,368, Bond (R-Mo) \$108,738, and in the House, Rep Waxman, (D-Calif) \$150,350, Fortney (Pete) Stark (D-Calif) \$144,751, and Gephardt (D-Mo) \$131,800. The total is \$1.4 million plus, and that is only health industry contributions for just 10 of 535 members of Congress. Meantime on Capitol Hill, the Senate adroitly avoided the question of Senator Packwood's alleged campaign deceit and lying. Term limits, anyone?

Addenda

- ▲ There are approximately 18 million impoverished people now blind from bilateral mature cataracts; most live in rural areas of the third world.
- ▲ A study revealed that 3% acyclovir or 2% trifluorothymidine used to treat herpes keratitis yielded no significant differences in healing time or success rates.
- ▲ Confused on the concept? Two Russian inventors requested a patent for an edible vodka bottle that, when digested, reduces the blood alcohol level in the body.

Aloha and keep the faith.

rts



**INOPERATIVE TRANSESOPHAGEAL
ECHOCARDIOGRAPHY**
(Continued from page 188)

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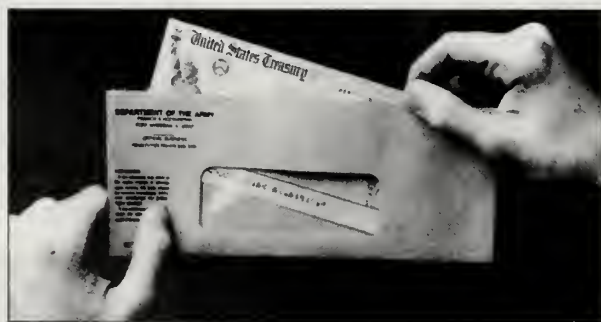
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PRAVACHOL® (Pravastatin Sodium Tablets) CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-24h} of pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a $\geq 50\%$ rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spiroglactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallenian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallenian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p < 0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/− mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses up to 50 mg/kg/day. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/m²/day). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial palsy), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, xanthoma, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecostasia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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Hawaii MEDICAL JOURNAL

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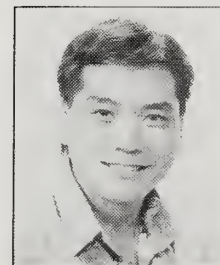
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Highlights of the HMA Council Meeting of June 4, 1993

Members present were: J Chang, President; A Don, F Holschuh, J Spangler, S Wallach, C Kam, R Stodd, C Lehman, M Cheng, R Goodale, P Chinn, W Dang Jr, P Hellreich, S Hundahl, K Thorburn, C Kadooka, H Percy, T Smith, J Lumeng, J McDonnell; Guests: Drs A Hawk, B Fong; Legal Counsel V Woo; F Reppun, Editor, *HMJ*; Auxiliary President, S Foo; HMA Staff: J Won, N Jones, L Tong, J Asato, J Estioko, and A Rogness, recording secretary.

The Secretary's Report and Treasurer's Report showed a marked decrease in HMA membership with dues down some 12% and about 100 dues-paying members to be dropped for non-payment of dues.

A letter was received from the president of the Hiroshima Prefectural Medical Association announcing the biennial visit of the Atomic Bomb Commission medical team to conduct examinations on A-bomb survivors, July 5 to 14, 1993. A luncheon will be hosted by HMA leadership to honor the team members and to rededicate the sister relationship established between the two medical associations many years ago.

The Membership Task Force is girding up for the next membership drive. Council approved a program in which senior HMA leaders will undertake a membership recruitment effort.

The Public Relations Committee chair, Steven Levine, reported that the committee has been successful in coordinating a health education television program. The Committee garnered KHON-TV2's support of the concept, and medical reporter Leslie Wilcox will moderate. The program is co-sponsored by HMSA and Longs Drug

Stores. HMA will not be liable for costs but will provide medical consultants, staff expertise and a phone bank of HMA members. Council approved the project. Physician members will be alerted and asked to serve on the phone banks to answer viewer questions.

Bernard Fong, chair of the Hawaii Foundation for Medical Care (HFMC), an affiliate of HMA, presented to Council a video and material relating to the Connecticut State Medical Society (CSMS) IPA (Independent Practice Association), an HMO. Council agreed that such an approach by a new entity might be the way for physicians in Hawaii to meet the challenges of health care reform both locally and nationally. It approved the creation of a separate, for-profit, capital stock corporation, to be owned by physician members of the HMA, in which physicians could have the control over their own practices and the future of physician reimbursement. HMA members will be kept informed of developments.

HMA's Hawaii Health Quest (the State of Hawaii's new proposal) Coordinating ad hoc Committee recommended that a letter be sent to U.S. Health and Human Services Secretary Donna Shalala reiterating the fact that Hawaii's physicians have always sought to provide their patients with the best in medical care and that the Hawaii Health Quest program was not discussed with physicians prior to its promulgation and has not been endorsed by the HMA; any program of this type needs input from Hawaii's physicians.

Fred Holschuh
HMA Secretary



Review of SHPDA

Former president of HMA Russ Stodd had been discussing SHPDA and the CON with David Hoff, editor of the *Maui News*. Hoff asked Russ to submit a contribution to the column headed "Viewpoint" in the *Maui News*. Russ promptly complied. It appeared in the 28 April issue.

Having obtained permission to do so, we are pleased to reproduce it in the pages of this *Journal*.

What's particularly tickling to our funnybone is David Hoff's comment, printed in the same issue:

"Doctor has the right perscription."

The column stated:

"We've never thought much of the State's archaic

Certificate of Need process, a gobbledygook of bureaucracy that gives thumbs up or thumbs down to proposals for new medical equipment or facilities...Maui eye surgeon Dr Russell T Stodd argues convincingly for the abolishment of CON. We second the motion."

The HMA Council, at its meeting on 7 May, unanimously voted to pass this message on to our readers.

The editor

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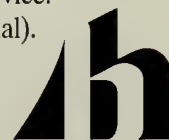
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Salmonellosis in Hawaii: 1987 to 1990

Hans E vom Dorp MD, MPH*

After an overview of salmonellosis, its epidemiology is described and techniques are discussed by which the disease could be brought under control. A review is made of all salmonellosis cases reported to the Department of Health Epidemiology Branch for calendar years 1987 to 1990. This data is compared with national and state laboratory data. Reports received by the Epidemiology Branch often lack sufficient information; this accounts for the sizable "unknown" entries. This frustrates a person's understanding of a more accurate incidence of the disease.

Introduction

Salmonellosis in Hawaii was reviewed comprehensively in 1984¹. The purpose of our report is to review the incidence and prevalence of salmonellosis in Hawaii from 1987 to 1990. The analysis is based on data from the reports of the Epidemiology Branch², the Department of Health annual *Statistical Report*³ and information from the State Laboratory⁴. A case of salmonellosis was defined by the isolation of *Salmonella* subspecies (spp) by a diagnostic laboratory.

Salmonellae infect humans as well as many species of animals. Identical serotypes can be found in both populations. Several taxonomic systems have been used to classify salmonellae with the most common method recognizing 3 species: *S. typhi*, *S. cholera-suis*, and *S. enteritidis*. The prototype of enteric fevers, typhoid fever, is caused by *S. typhi*, found only in humans⁵. All other salmonellae infect both animals and humans with more than 2,000 species (serotypes) of *S. enteritidis*. *S. enteritidis* subspecies are usually referred to by their subspecies name only, eg *S. typhimurium*, *S. arizonae*, etc. *S. cholera-suis* can be responsible for generalized *Salmonella* septicemia with focal lesions to be found anywhere in the body. Most large outbreaks of salmonellosis involve one of the *S. enteritidis* serotypes.

Epidemiological investigations show that outbreaks of the disease often are attributed to improper food processing, food handling or storage. At any point from food production to food consumption, contamination with salmonellae can take place with human infection as a result.

Salmonellae are killed readily by heat at 55°C (131°F) for one hour or in 15 to 20 minutes at 60°C (140°F)⁶. The length of time the food item is heated affects the degree of penetration of the heat. An unthawed piece of meat or packaged food will obviously heat unevenly with the cooler core likely to provide a nidus for possible later contamination. Animal salmonellosis can lead to human infection if meat, meat

byproducts or eggs are cooked only partially, or if milk is not pasteurized. *Salmonella* contamination of meat and eggs can be deep-seated and good heat penetration is imperative.

Salmonellae can spill from animal viscera and feces during the preparation of carcasses in the slaughterhouse, during the milking of animals, or by fowl while they lay eggs. The bacteria can course through the blood of poultry and be present within the magma of eggs. With the introduction of antibiotics into animal feeds, the resistance to antibiotics by Salmonellae has increased. Domestic fowl probably constitute the largest single reservoir of salmonellae⁶.

A recent investigation of an outbreak in Hawaii established that 9.43% of the eggs randomly sampled in Honolulu supermarkets were contaminated on the shell surface by salmonellae⁷. Further investigation pinpointed a producer's faulty egg-sanitizer's temperature-control mechanism as an etiological factor. In that report, the investigator correlated 16 cases of salmonellosis in 1989 with serotypes isolated from eggshells⁷.

For the sake of expediency, foods often are prepared long before they are consumed. In order to avoid overcooking, these foods are often kept at low heat, thereby ensuring an ideal medium for bacterial growth and then quickly re-heated before serving. The USDA recommends that thorough reheating of previously prepared foods be done at 165°F or higher before being served⁸.

In reported outbreaks of salmonellosis, the implicated food was frequently prepared early in the day before being consumed several hours later, either without adequate refrigeration or without proper re-heating. Both proper heating and refrigerating can effectively attenuate the presence of Salmonellae. *Salmonella* overgrowth is kept at a minimum at temperatures below 5°C (41°F).

For transient, uncomplicated enterocolitis caused by one of the *S. enteritidis* spp, specific medication is generally unnecessary and treatment is supportive, consisting only of rehydration and electrolyte replacement. The use of antibiotics may help propagate resistant strains and increase the likelihood of a carrier state. Since the biliary tract is usually unaffected by gastric acidity, yet proximal enough to the GI tract, its higher pH can provide a refuge for Salmonellae, especially *S. typhi*. Cholecystectomy is generally curative for up to 80% of the population of carriers⁹.

Although most human infections with *salmonella* spp are self-limited and often unreported, the cases presented to health services frequently involve very old or very young people. In such cases the morbidity may be significantly high.

Discussion

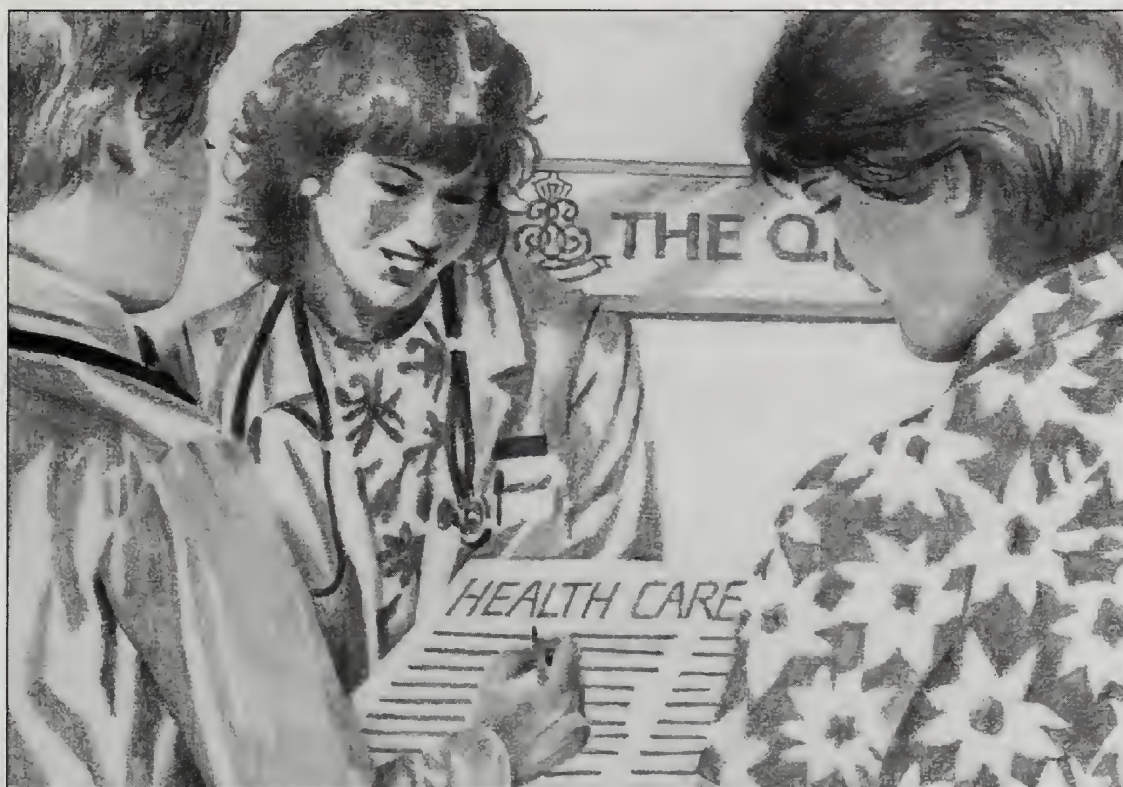
Incidence

When the rates for salmonellosis are compared by year for Hawaii and the nation, Hawaii has an incidence nearly 2 1/2 times that in the nation as a whole (Table 1). Hawaii's

(Continued on page 212) ►

* Hawaii State Department of Health
Communicable Disease Division
P.O. Box 3378
Honolulu, Hawaii 96801

Received for publication June 6, 1991



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SALMONELLOSIS IN HAWAII: 1987 TO 1990

(Continued from page 210)

Table 1:

Comparison of Incidence Rates
Hawaii and Nation: 1987 to 1989

State of Hawaii	Nation
1987 42.6/100,000 population	1987 42.6/100,000 population
1988 44.07/100,000 population	1988 17.809/100,000 population
1989 33.0/100,000 population	1989 16.8/100,000 population

*Source: Statistical Report, DoH and State Laboratory

**Source: Annual Summaries on Salmonella Surveillance, CDC, 1989

Table 2:

State of Hawaii, Incidence of Salmonellosis
Serotype* and Calendar Year
(reporting restricted to 10 or more cases per year)

Serotype	Year			
	1987	1988	1989	1990
Agona	15	14	13	16
Anatum		25		
Berta			12	
Enteritidis		13	12	
Hadar		19	21	15
Heidelberg	38	31	56	30
Infantis				16
Muenchen		13		16
Newport	15	19	10	16
Oslo		12		
Oranienberg		22		
Panama			11	
St Paul			13	13
Typhi, Phage Types A, M, E & E1				12
Thyphimurium	27	123	35	107
Thyphimurium var Cop			22	37
Weltevreden	29	70	66	40
Montivideo	10		10	
Unreported serotypes	261	23	4	9
Others (incidence of 9 or less cases reported)	67	138	102	120
Totals Cases	462	522	387	447

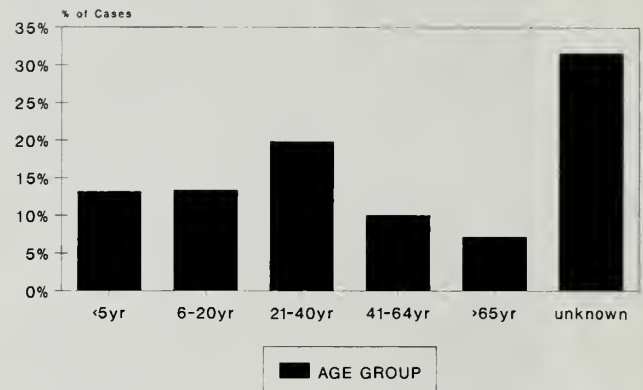
*Source: Statistical Report, DoH and State Laboratory

**Source: Annual Summaries on Salmonella Surveillance, CDC, 1989

rate in 1990 was 39.3 per thousand persons. At the time of this writing, national figures for 1990 have not been published.

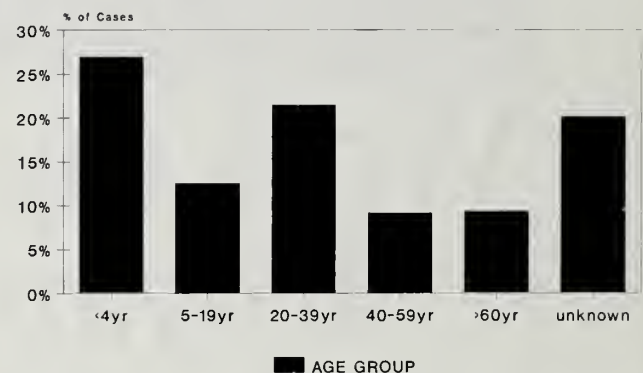
What accounts for this higher incidence of salmonellosis in Hawaii when compared with the rest of the U.S.? One suggestion is that our small population base and small geographic size results in better surveillance than in the rest of the United States. Cultural food preferences and sites of food consumption might be other factors contributing to the high incidence of the disease. Another contributing epi-

Figure 1
Age Distribution (%) of Salmonella Cases
Hawaii, Calendar Year 1987



Source: Epidemiology Branch

Figure 2
Age Distribution (%) of Salmonella Cases
Nation, Calendar Year 1987



Source: CDC

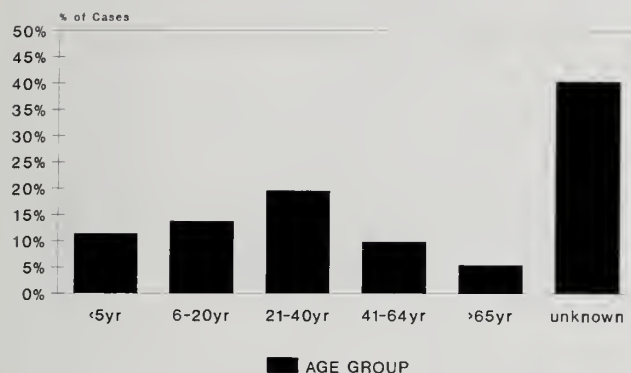
demiological factor is that salmonellosis reporting is mandatory in Hawaii.

Seasonal variation

The date of onset of the disease is usually not submitted to the Department of Health (DoH); hence, temporal analysis can be done only by the time and date of the report. A time lag of not more than one month between date of onset and date of report was usually observed when dates of onset and dates of report were both available.

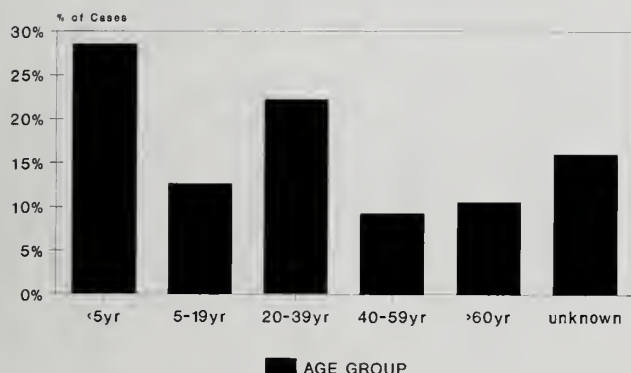
Dates of reporting by months of confirmed Salmonella cases to the DoH are shown in Figure 8. Note the consistently low level of incidence for a period of approximately 8 months, and an increase during the summer and autumn months. There has never been an explanation for this observation except that it might be attributed to increased recreational activity, an increase in tourism and the greater consumption of *picnic-type foods*, traditional among Hawaii residents during those months.

Figure 3
Age Distribution (%) of Salmonella Cases
Hawaii, Calendar Year 1988



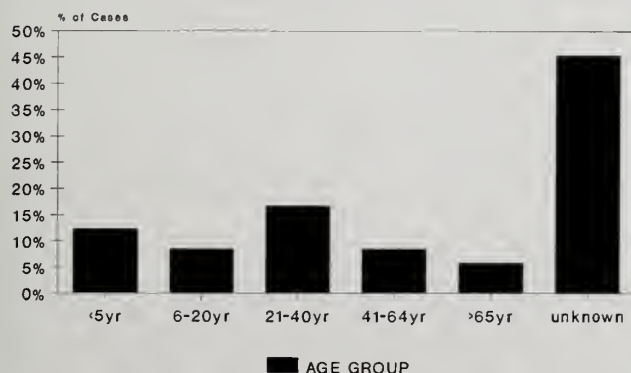
Source: Epidemiology Branch

Figure 4
Age Distribution (%) of Salmonella Cases
Nation Calendar Year 1988



Source: CDC

Figure 5
Age Distribution (%) of Salmonella Cases
Hawaii Calendar Year 1989



Source: Epidemiology Branch

Age

National data for 1990 are not available at this writing. It was possible to compare only state and national age distribution statistics for 1987 (Figure 1 and Figure 2), 1988 (Figure 3 and Figure 4) and 1989 (Figure 5). The <5-year-old group is a smaller percentage of the total reported cases in Hawaii accompanied with the cases in the U.S. in both 1987 and 1988. A smaller percentage of cases among the younger than 5-year-old group is unexplained but it may be accounted for by the rather large numbers in the category labeled "unknown age".

Serotypes and their relationship to etiology

The most frequently occurring serotypes for Hawaii are listed according to the number of human cases of salmonellosis reported (Table 2).

It has been difficult to correlate particular serotypes of *Salmonella* spp with particular foods, since laboratory and epidemiology reports generally do not indicate the source of the infection. However some serotypes are generally associated with particular animal reservoirs. For example, in the 1987 barbecued chicken outbreak¹⁰, the 67 culture-confirmed cases were of the *S. agona* serotype, commonly found in poultry. Poultry flocks also may be heavily infected with *S. typhimurium*¹¹.

In preparation for the annual Honolulu Marathon in early December 1987, a high carbohydrate meal was prepared for the contestants several days before the event. This banquet meal resulted in 288 clinical cases of Salmonellosis with eventual laboratory-cultured confirmation of 25 cases. *S. weltevreden*, a common serotype in Hawaii, was cultured in all of the confirmed cases¹².

Apart from a few isolated incidents in which a particular serotype was responsible for a large outbreak of disease, it is difficult to associate specific serotypes with particular foodstuffs in Hawaii. Investigation into this area might help to reduce the disease outbreaks.

Reporting

A more accurate understanding of salmonellosis in Hawaii has been frustrated by incomplete communicable disease reports submitted to the Epidemiology Branch. These reports are required to be submitted by physicians, clinics and hospitals as soon as possible after the diagnosis of a reportable disease. The misleading or incomplete information provided in these reports is evidenced by the category of "unknown age" in the reports.

On the national level, the younger-than-5 age group accounts for more than 25% of the total cases of salmonellosis¹³. Available figures in our Epidemiology Branch account for less than 15% of all cases under age 3². On the other hand, State Laboratory reporting shows high levels of incidence among the younger age groups during fiscal year (FY) 1987 to FY 1990⁴. The majority of these cases in the ≤age-3 group show a mean percentage of 38.02% of the total number of cases reported over the 4-year period (see Figure 6). These figures are higher than the reported national percentage totals for the respective age groupings. A comparison between these reported percentages is highlighted in Figure 7.

(Continued) ➤

Conclusion

Although surveillance data can provide a basis for policy, if the data are incomplete because of poor reporting practices, conclusions about the existing data can be misleading. In order to accomplish a more comprehensive survey of salmonellosis in Hawaii, it was necessary to compare the available data in the Epidemiology Branch² with that in the State Laboratory⁴ and in the Centers for Disease Control (CDC) *Annual Summaries on Salmonella Surveillance*¹³.

Better cooperation is needed between the Hawaii DoH and the medical community in the direction of better reporting procedures. These should be honest, complete and provide only pertinent information; they should be submitted on a timely basis.

Consistently good reports should receive accolades; poor reports should be singled out for follow-up with suggestions to the reporter for improvement.

It is usually the responsibility of public health workers to determine the causative factors of a disease outbreak and to initiate control measures to decrease morbidity and mortality. However, common sense dictates that greater attention to very simple and yet effective measures of food preparation and storage by the general public can decrease the incidence and prevalence of the disease in Hawaii. As has been pointed out in this discussion, meat, chicken, eggs and milk account for most of the outbreaks of infection by *Salmonella* spp. Often this is a function of the lengthy journey from field and farmyard to the eating table.

Although most people have little control over the production of food, there is a degree of control that people can exercise over the subsequent storage, handling and ultimate serving of food.

Because salmonellae are ubiquitous in our environment, the general public needs to be aware of the problem. Its role in preventing infection within the home and in dining establishments needs to be emphasized.

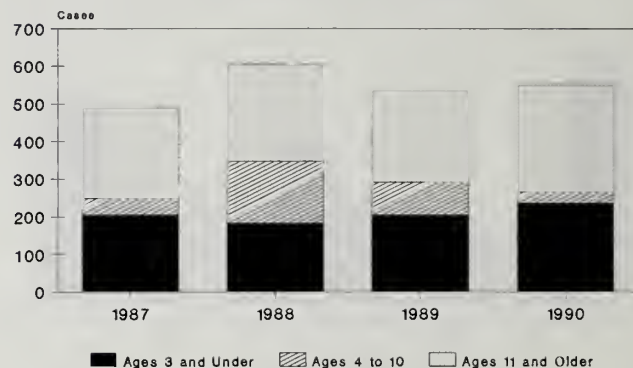
ACKNOWLEDGEMENTS

Suggestions about the subject and subsequent review of this material have been made by Eugene Pon MD, Henri Minette, DPH and David Sasaki DVM MPH of the State Epidemiology Branch and Al Katz MD, Professor of Epidemiology at the University of Hawaii, School of Public Health. Their recommendations are appreciated. Thanks also are extended to Mr. John Tawney for his assistance in putting the manuscript together.

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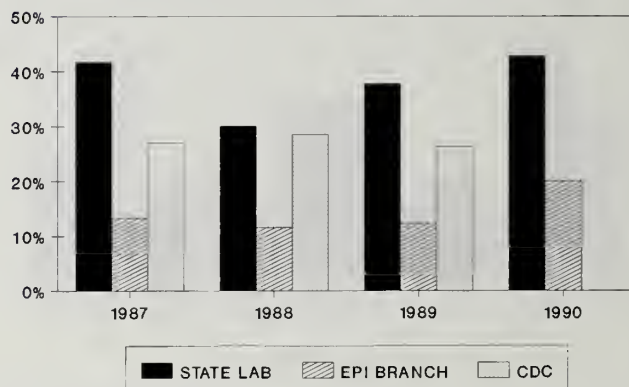
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Figure 6
SALMONELLOSIS STATE LABORATORY REPORT
FY 1987 to FY 1990



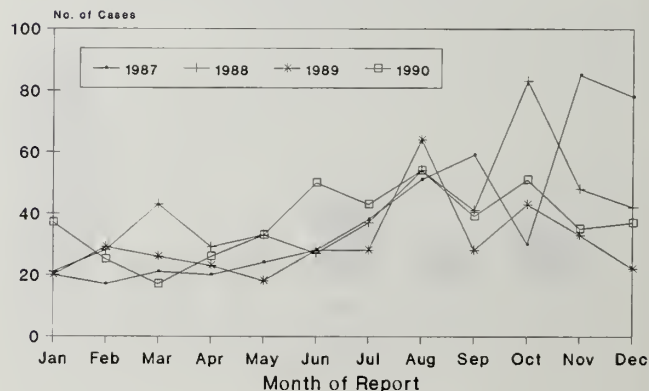
SOURCE: Hawaii State Laboratory Reports

Figure 7
Comparison of Salmonellae Reports
Incidence in Children: 5 years & younger



SOURCE: State Lab, Epi & CDC Reporting

Figure 8
Monthly Incidence of Salmonellosis
Hawaii, 1987-1990



SOURCE: Epidemiology Branch

(Continued on page 226) ►



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One Rx for Solo Survival

Linda "Fritz" McKenzie JD*

The Clinton administration's prescription for the "health care crisis" that was a hot campaign topic will be forthcoming. Mrs. Clinton is not backing away from the 100-day deadline set by the President. Hillary has already begun to focus on some of her big hits, if one can believe the media reports about her comments related to drug companies. The months ahead will be crucial for solo and independent physicians and should be used by them to prepare for a change in how they practice medicine. The following article suggests one area to which they may choose to direct their energies.

Hardly a publication can be read without being confronted with "THE HEALTH-CARE CRISIS".

All national media; locally, our news items and editorials, even local CPA's newsletters seem to focus on health-care and its costs. Obviously an industry that commands almost 14% of the gross national product in an economy that is at best sagging and is at least sad will attract a plethora of specialists and consultants who have ideas and solutions.

The vast majority of physicians feel besieged and beleaguered by a new onslaught of would-be authorities telling them how best to care for their patients. It's not enough that insurance carriers, governmental state and federal agencies, and legislative bodies have all decided to have their input into what at one time was a very private matter between physician and patient. Now we also have consultants and politicians, and let's not forget the opportunists, who have jumped on the health-care bandwagon.

So where does all of this leave the MD who for years has been out there delivering or attempting to deliver health care in the same doctor-to-patient manner that doctors for centuries before have done? With the cry for managed care, better utilization and more scrutiny in all aspects of the delivery of health-care and the additional demands on physicians' time, perhaps the most urgent question is where does this leave the solo practitioner? Many will say: "Nowhere!" History tells us that this is probably not true. People will tolerate just about anything except "messing with their health care" and most, in the final analysis, do not want it delivered like their supermarkets serve up packaged goods, nor to be served the same way they would receive a meal at a fast-food place. They want individualized, personal care.

So what is the lone soldier of medicine or the small group to do? I am not fond of framing references in terms of war, but it seems to be an analogy with which many physicians can relate, given the present day health-care climate in which many of them feel they are forced to function. Does the lone MD throw in the weapon, surrender and go to work for a

hospital or HMO; or retreat to the ivory towers of academia and tell everyone else how it should be done; or become a high school or college biology teacher, pharmaceutical representative; or simply take early retirement and fish or golf every day instead of only on Wednesday?

For younger physicians, most of these options are not available, at least for the ones with visions of practicing solo. There are not a lot of alternatives for many physicians. MDs come from a school of focused learning that leaves them with very few job skills for the marketplace other than practicing medicine or teaching it. In fact, many are still attempting to repay their debt for the privilege of spending 20-plus years in the educational process and earning the right to place "MD" after their surname. For these brave souls attempting to wing it in the marketplace, what can or should they do?

My suggestions have not changed from the message I have attempted to deliver on every occasion the past decade when I have spoken to and with physicians and/or their spouses, particularly those responsible for managing their physician-spouse's practice.

One thing is certain: What medical school did not and does not do is prepare students to be business managers. Admittedly a few are gifted with a good business sense, but they are rare and often accused of neglecting the medical and personal part of their practice if and when they become overly involved in the business end of it.

Again, what can be done to allow that group of individuals who choose to practice in a solo environment to continue to do so? Throughout the history of this nation autonomy has been precious in all aspects of the American society and perhaps most in the areas of entrepreneurship and medicine. How can physicians maintain their independence and still survive financially in the new models that are being touted, perhaps dictated, by those in control and by the economy itself?

The very first step to be taken must be to make a clear and realistic assessment of how the practice, and particularly the office, is being managed and by whom. How are personnel being utilized; how is technology being utilized; what if anything can the physician do to manage time, deliver quality care and still be cost effective.

Historically, most physicians have not had to pay attention to the bottom line, as all other business people must do. Business acumen was never high on most physicians' priority lists. As a matter of fact, those in the profession who did pay attention to such matters weren't always terribly serious about focusing on a well-run and cost-efficient office. Mediocrity and make do were the watchwords in too many instances. Now a qualified and skilled coding expert on the staff has taken on new value. An organized and experienced office manager has become a highly sought individual; and, if either or both of these happen to be an interested spouse, the physician is sitting on a virtual gold mine. The inherent

(Continued on page 218) ►

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"These are good times to test a bank's financial services," said Ronald Migita, the man most directly responsible at Bank of Hawaii for delivering the goods. "When the economy slows down, everybody has to be a little more careful — a company of what it spends and a bank of what it lends."

Liberty Bank's Milton Zane is more direct: "Times like this separate the men from the boys." That goes for both businesses and bankers.

Hawaii's economy has been in a slow- or no-growth mode for the last two years. Bank economists expect more of the same this year. Against a backdrop of the kind of expansion the economy has experienced in the 34 years since Statehood, a three-year period of even slow growth can seem to many like a full-scale depression.

But it isn't, and the outlook is for improvement next year. In the meantime, Hawaii's small businesses, which make up the vast majority of all businesses in the state, are tightening their belts, rethinking their game plans and looking for all the help they can get — "as long as it doesn't cost anything," said Bank of Hawaii vice president and small business advocate Robert Fujii. "Everybody's hanging on to their cash."

Even so, bankers agree there's plenty for them to do. One expressed the opportunity this way: "We have the chance to get to know our clients, spend a little quality time with them," said Central Pacific Bank's Wayne Kirihara, a marketing man. "We may not be able to help them now with new services, but, in knowing them better, everybody benefits eventually."



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Raising Money

Even continuing low interest rates aren't coaxing many small business borrowers to take on more debt, but many companies have been taking advantage of conditions over the past year or more to restructure existing financing. Bank of Hawaii senior vice president Ron Migita says the bank's credit policies are unchanged despite the economic slowdown, but there's no rush to borrow. "We've got plenty of money to lend, but it's a cautious world out there," he said.

Even the pace of refinancing — substituting new, lower-interest loans for old, higher-rate paper — has slowed somewhat, according to Pioneer Federal Savings Bank executive vice president Al Yamada. Though referring primarily to the mortgage financing done by Pioneer, he says refinancing volume is down from a year ago, even six months ago.

But GECC Financial Corp. vice president Lester Shoda, who heads that finance company's Pearlridge branch, says some small business owners are rearranging their loans to take advantage of today's low rates. "We're seeing some refinancing," he said. In the beginning of the year, we noticed many homeowners were taking out building permits for construction and home additions. We also heard homeowners and general contractors mention that they were frustrated with their lenders

because of the delay and amount of paper work that was required to obtain loan approval for home renovations.

GECC hopes to change that come late August, when it launches what it's calling its "Remodeling Equity Loan" program. Though aimed primarily at homeowner interested in expanding or renovating their residences, the program is a new wrinkle in the home equity credit line services originated by GECC some years ago.

Under the program, consumers can use the existing equity in their home to do any type of renovation— room and bathroom addition, repair and upgrade that kitchen, install a swimming pool. It will increase the value of the home and at the same time save the homeowner money. It is a simplified construction loan program up to \$100,000 or more where no bond will be required as long as there is no major structural change to be done to the home. Besides this savings, our program does not charge you any points and if you qualify, no appraisal may be needed. In fact, we can even include bill consolidation without refinancing the homeowner's existing first mortgage. At the same time, our Remodeling Equity Loan offers flexible repayment plans which makes it easier for the homeowner to qualify. Our Remodeling Equity Loan program welcomes investors as well as owner occupants.



"One of the keys to operating in an economy like today's is flexibility," said Chow. "You have to be innovative in your approach to things, ready to seek out the things that work best under the circumstances."

Adjusting to the Times

"Whenever times get uncertain, most businesses instinctively pull in their horns," said Winston Chow, executive vice president at First Hawaiian Creditcorp, a unit of First Hawaiian Inc., parent of First Hawaiian Bank. "We're seeing mostly debt restructuring among the small businesses we deal with," added Chow.

Larger institutions like First Hawaiian Bank and its affiliates offer an array of business services. They extend far beyond business loans — to areas like credit card, payroll and other cash management services — but traditionally tend to cluster around lending. In that field there are a variety of loan types: credit lines, short-term corporate loans, commercial real estate loans, and more.

First Hawaiian Creditcorp has done a lot of "land loans" in recent years — loans on purchased property to finance home and other construction. These can be used simply to build on the property — often times at a lower cost and more suitable design than buying existing homes — or can be combined with permanent financing, a mortgage on the finished development. The credit company belongs to the Hawaii Community Reinvestment Corp., a local agency that helps fund affordable multi-family housing, and has done land loans through this program.

Executive vice president Chow says

many business owners have used such real estate financing to restructure their companies' debt. "With today's low lending rates, especially on long-term real estate loans, people are paying off their short-term, higher-cost debt with the long-term loans," he said. "The savings to cash flow can be substantial."

"One of the keys to operating in an economy like today's is flexibility," said Chow. "You have to be innovative in your approach to things, ready to seek out the things that work best under the circumstances."

A Way to Keep Up

One such innovation might be avoiding the often high cost of buying capital equipment by leasing it. The rapid changes being forced on many industries by technological developments, coupled with keen competition in every marketplace, makes maintaining state-of-the-art equipment a must in most businesses. Letting a competitor get the jump on you with the latest development in, say data processing or telecommunications, could be very costly. Yet, the expense of keeping up with technological change can be beyond the reach of a struggling business, what with all the normal operational demands on cash flow. Leasing the new equipment could be the answer.



First Hawaiian Leasing Inc., another subsidiary of First Hawaiian Inc., does a lot of its business with companies trying to keep up with the obsolescence built into today's high-tech equipment by manufacturers and caused by sudden breakthroughs in the market. Once, capital equipment would serve a business at least as long as its depreciation schedule. But, where much of the high-tech equipment is now concerned, this is no longer true, according to First Hawaiian Leasing executive vice president Steve Marcucilli.

As a result, companies have had to adjust their thinking. "They're learning that it isn't ownership of equipment as an asset that's important, it's the contribution the equipment makes to cash flow that counts."

"In today's marketplace, a computer system may last no more than five years, at the rate advances and new product development is taking place," said the executive. "Maybe not that long, if new software or peripheral equipment comes along that won't fit your system. You then have a choice. You can either trade your system in on a new one that uses the latest developments, or you can try to make do while your competition is taking advantage of the new developments. Sometimes, you can't afford to sit tight without losing business," said Marcucilli.

First Hawaiian Leasing handles a wide assortment of business equipment, from cars to computers. The savings it offers customers goes beyond the cash flow advantages of leasing over owning the equipment. The price and tax breaks the leasing company realizes by being the equipment owner and buying in quantity are savings that are passed on to customers in lease rates, an option that can save them cash and

offer other advantages.

But even equipment cost savings are affected by business slowdowns.

When revenue declines, so does everything else on an income statement. Bankers say the current business slump has affected the need for new capital

equipment, something leasing agents say has slowed consumption.

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Robert Tsukada, a vice president at American Savings Bank, says the best



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"In today's marketplace, a computer system may last no more than five years, at the rate advances and new product development is taking place,"

way he can characterize the climate for bank services is "cautious." "There's across-the-board caution," he said. "It isn't that they don't want or need the services, it's that they don't want to do anything that might end up costing them more money."

This has created an opportunity for bank lending and branch officers to get to know their business clients, Tsukada and other bankers say. "We encourage our people to talk to their business customers," said Liberty Bank's Milton Zane.

One reason: "We want to know as soon as they start having problems," said Wayne Kiriara, of Central Pacific Bank. But the reason isn't just defensive. "Maybe there's something we can do to help them."

"We tailor our business to small business," said Zane. "Many business owners know the products and services they sell better than their business itself. Maybe they're great auto mechanics, but not very good business administrators. Helping them succeed is a challenge for a banker. You have to get a little involved. If you don't, and the client goes out of business, both you and the client lose."

"We're giving a lot of individual attention to our business customers," said CPB's Wayne Kiriara. "These are hard times for many small businesses. They're now catching a softness that's been rippling through the economy

since 1991. First to be hit was tourism, then retailers, now small business people in general. They need all the attention we can give them."

The main focus of such help is cost containment, says Kiriara. "People aren't making any major moves in their business, no big commitments. They don't want to do anything that's going to mean a jump in costs. Most are hanging on, cutting costs where they can, waiting for the economy to improve."

The situation gives banks an opportunity to get to know their clients better, says the CPB executive. "We're telling our branch managers and loan people to spend time with their clients, even if there's no business to conduct with them. Get them to tell you about their business, discuss their problems. Maybe there's something we can do — cross-selling our services. Call it micro-marketing. Maybe the best thing we can do is listen."

American Savings' Bob Tsukada notes that the economy has led to a slowdown in loan demand, as well as some tightening in credit. "Basically, we're just being cautious like everybody else," he said. Since much of the bank's contact with business clients is through its 45 branches, he also says this is a good time for both sides to get to know the other better.

"Just filling out a loan application can be an enlightening experience," says



Tsukada. "The borrower can find out a lot about his own financial needs and so can his banker. Even if the loan isn't approved, it's an educational experience that will pay off later."

There's a science to filling out such applications, Tsukada and others say, that is helpful not only to the lender but the borrower as well. "Going through the discipline of filling out an application, including assembling the information you need, tells a borrower something about his own cash needs."

Tailoring the Service to the Business

Tsukada, who heads American's corporate banking department, says his operation deals with many professionals as well as business people. The association has made business loans for only about a decade, so he says it's still expanding in the field, although Tsukada says it never wants to grow to the point that it loses the personal touch that he feels is essential in business as well as consumer banking."

Serving professionals' financial service needs has become something of a specialty. "People tend to forget that their doctor, lawyer, or accountant are in business the same as they are," said Tsukada. "No matter how skilled and successful they are in their practices, if they ignore the business side they're in trouble sooner or later. A doctor needs financial services the same as a building contractor or a manufacturer, they're just a little different."

"We've spent time in the field familiarizing ourselves with those differences and I think as a result we've built a good business with professionals," he said. "Each is different and working with them helps us make a practice of tailoring our ser-

vices to the business we're dealing with. That's important with all clients."

Cash Flow is What Counts

A number of institutions offer counseling services on top of specific services

like payroll handling. Bank of Hawaii, the state's largest bank, probably offers the most extensive battery of small business services.

Bankoh organizes its business client relationships on levels. The levels are based on size of sales. "We care most about



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"People tend to forget that their doctor, lawyer, or accountant are in business the same as they are,"

cash flow," said Ron Migita, who is in charge of the bank's business lending and related activities. "Some loans are based on assets, like real estate loans. We're interested in the cash the business generates."

Bankoh's 100 or more individual branches usually handle business clients that have up to \$2 million in annual sales. Those with sales of \$2 million to \$10 million normally work through the bank's network of Business Banking Centers — one-stop financial service operations that offer all the bank's business services under one roof. There are three centers on Oahu, and one each on the islands of Maui, Hawaii and on Guam, where Bank of Hawaii has a large presence. Larger accounts are handled by the bank's corporate banking office in Honolulu.

Bank of Hawaii has the most extensive international banking operations in Hawaii. It has branch or representative offices in the South Pacific and in most of the banking capitals of Asia. Bankoh's international division, based at its Honolulu headquarters, provides a full line of financing and other services for international clients.

But, according to Ron Migita and Bob Fujii, the bank's small business advocate, such diversity hasn't diminished the bank's attention to the business that is still its foundation, serving


Hawaii customers. Creation of the systemwide business banking centers is an indication of this commitment.

The Bankoh business services run from business checking and savings accounts to usual loan and other credit services, credit cards, payroll and other cash management services, and access to the bank's large international department. The bank even has a factoring operation to help businesses with their cash flow.

The Bankoh family of institutions includes trust operations, led by Hawaiian Trust Co. These services are being expanded greatly with the acquisition of American Financial Services of Hawaii, parent of Bishop Trust Co. and American Trust Co. Bishop and Hawaiian Trust have long been the leading full-service trust operations in Hawaii and their combination will give Bancorp Hawaii, Bank of Hawaii's holding company, a dominant position in the Isle trust business.

The trust companies offer assistance in managing employee benefit accounts and other administrative and advisory functions to corporate as well as individual clients. Both have experienced research departments well qualified to manage all types of investments. American Trust specializes in depository trusts, such as employee profit-sharing and similar plans whose investments are managed by others.





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"Of course, you never know," cautioned Yamada. "If I knew for sure what interest rates were going to do I'd be sitting on the beach sipping a mai tai."

Decentralized Services

First Hawaiian Bank and its family of service companies puts more emphasis on the branches, with backup from the head office. Being Hawaii's second-largest bank, FHB provides the full gamut of small business services, augmented last year with the bank's acquisition of the former First Interstate Bank of Hawaii, an institution that specialized in working with small businesses. First Hawaiian is also in the process of acquiring Pioneer Federal Savings Bank, which will expand its already sizable mortgage loan activities.

Central Pacific Bank's Wayne Kiriara says niche marketing is what banking is all about these days. Small businesses are one of CPB's niches. "This is what business is in Hawaii," he said. "Ninety-five percent of your corporate business is with small businesses. You have to tailor your services to their needs."

Most banks say they are positioning themselves for the economic upturn that they hope will happen next year. Loan volume is by and large flat, with occasional upticks — which, all hasten

to say, are better than downticks.

"Slower loan volume doesn't mean slower business activity," said Pioneer Federal's Al Yamada. "We're still making a lot of loans and that may pick up when people decide interest rates are about to head up again."

But Yamada and others think rates will stay at present levels for the rest of this year. "Of course, you never know," cautioned Yamada. "If I knew for sure what interest rates were going to do I'd be sitting on the beach sipping a mai tai."

Bank of Hawaii says its volume in SBA loans — loans backed by the federal Small Business Administration — is actually up this year, but SBA loans are difficult to obtain because of their qualification restrictions.

A sign of the times: Bank of Hawaii says there's been some weakness in its payroll services to businesses, including automatic paycheck deposits. "When times are tough, people want to see their paycheck, not just get a deposit slip," said Bob Fujii, who recently won the SBA's "Minority Small Business Advocate of the Year" national award.





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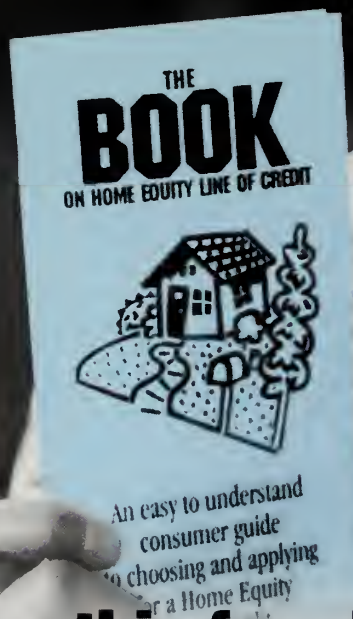
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problem in the latter instance is any personal strife (and there will surely be some) that living and working together brings into being.

A recent article in the *Wall Street Journal* commented that none of the above measures, nor any consultants, are going to be able to solve the real problem of declining reimbursements. Most or at least many physicians are already working at peak productivity and there's not a great likelihood of increasing quantity in many offices. Reimbursement has become a territory controlled almost solely by insurance carriers, government, and the marketplace. Physicians rarely count for much in this process. Will this scenario become more true in the future? I think so.

Where then will this leave solo practitioners or small office clinicians, and what means will be left to them to enable them to continue "winging it" alone if they choose to do so? The answer clearly and simply is that physicians must focus on establishing and maintaining lean, efficient, well-organized and well-monitored practices. The one thing the physician still controls is the staffing of the office, procedures and overhead expenses.

To accomplish this "lean machine", where does one begin? First, by recognizing that overstaffing and assuming that work is done efficiently and cost-effectively are luxuries that can no longer be part of the modus operandi of physicians' offices. Good business practices must be followed.

The luxury of having multiple offices with the inherent duplication of supplies, staff and other expenses, and waste of valuable time will need serious assessment to justify the continuation of those offices. The value of multiple offices must be weighed against all these offsetting expenses. What criteria do we use to make those decisions? The logical starting place would be a survey of the patient population. Simply ask: "Would you stay in my care if I centralized my practice?" If the answer is, "Yes", why not consolidate? We know that in most instances efficiency comes with consolidation if it is implemented correctly. On the other hand, if patients are resistant to traveling any distance, that second office is needed. Look to every possibility of consolidating what can be shared and streamlined, thus avoiding duplication as much as possible.

Certainly computerization should help to accomplish both efficiency and elimination of duplication. Technology is definitely a tool, if used correctly, that could be tremendously helpful in achieving the goals of an efficient and cost-effective office. With the wave to change to electronic data submission and fund transfer, technology must be considered. However, technology is dependent upon people, beginning in the implementation stages and continuing through the managerial area of a practice. Those resisting computerization are fighting a losing battle because all the *powers* in industry, business and politics have identified the paper problem as the first foe to attack in the realm of administrative changes. As painful as it will be, it is the coming thing and physicians had better be prepared.

There are many products offered, ill-chosen ones will only come back to haunt you. Both physician and manager should spend time in choosing the technology that will launch them into the new wave of claims, remittances and electronic fund transfers. Many offices that are already computerized will have to upgrade to accommodate the changes in the industry. This is an inherent problem faced

by an industry exploding with knowledge and advances every day.

Given the almost unlimited products available, for what should the physician and manager be looking? My first suggestion is a program that will not be antiquated within a year, one that has the ability and flexibility to change. Most important, it must allow for inexpensive change so that the budget isn't whacked everytime a new technology is introduced in the market, or a carrier or the government changes coding or other requirements.

Second look for a product that is supported by a company that will be able to respond to your needs effectively, quickly, efficiently and comprehensively. Look for a vendor or company that is committed for the long haul to the medical profession and has depth and experience in a wide range of fields applicable to technology for use in the medical office. Each practice will have its own special needs and weaknesses and these should be considered in implementing the choice.

Very important in the choice of a technology is whether it allows for the maximum flexibility in the Hawaii market. We know there is a dearth of experienced workers in the medical field so a system that will allow maximum flexibility in hiring and training employees is essential. The feature to look for in a system would be one that has tremendous capability of being "smart on line", ie one that has many checks and validations that remove the margin for error in the input of data.

Physicians need to relearn and rethink all the options available to allow them to maintain a degree of autonomy. Too often I have seen offices that become totally dependent on one or two employees. If possible, employees should train each other to do the job equally well.

Independent physicians choosing to continue solo practice and still survive in the managed care climate (that we know will come, for better or worse) must have the ability to network and connect with other solos and small groups in order to negotiate with carriers and employers for a patient base. The best way to do that is to have a well-run, well-strategized office that uses state-of-the-art technology and an office that is efficient and cost-effective. The managed care concept is here. The varied ways in which to become a player in this new format of delivering health care can be accomplished by joining PPOs, HMOs, networks, foundations or whatever other creative modes that yet may come. Every physician must acquaint herself or himself with these new concepts of delivering health care to patients.

Change within the health care system has been volatile. In the 1960s there was the advent of specialization, sub- and sub-sub-specialization of medicine. There was a demise of family practice. Now, as we enter the 1990s, we see the demand for family practice *specialists* far out-pacing the available supply and the educational system's rate of production. What has remained a constant, however, is patients' demands for medical care that is immediately available when the crisis strikes, and the need for kind and caring healers. The method whereby this will be delivered can change, the environment can change, the emphasis or focus can change, but the hoped for end-results will remain constant.

Physicians' practices will be the primary targets of changes within the health care industry and in revamping the health care delivery system. Physicians must be prepared,

(Continued on page 226) ➤




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In Pursuit of Excellence: A Model of Collaboration for Nurses at Hawaii State Hospital

Charlotte MF Trotter RN, MS*

In 1989 the Hawaii Medical Journal devoted an issue to the status of mental health in Hawaii and mental health leaders in the State criticized the lack of involvement by the University of Hawaii^{1,2,3}. This paper is written in response to the challenge and will discuss a dynamic model based on collaboration between the Hawaii State Hospital (HSH) and the School of Nursing of the University of Hawaii (SoN), that was implemented in September 1990. Since the publication of Magnet Hospitals. Attraction and Retention of Professional Nurses⁴ there has been much interest by service organizations in defining the factors that build excellence⁵.

Background

In 1974, HSH lost its accreditation by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). One of the reasons cited was the shortage of nursing staff. Since 1986, Hawaii has ranked 51st in the nation in terms of the quality of care and services delivered in the public sector to the disenfranchised who suffer severe forms of mental illness⁶. The United States Department of Justice (DoJ) examiners continued to monitor the mental health system and services at HSH, which they found alarmingly deficient in terms of the settlement agreement^{7,8}.

Mental health is a major public health issue. Alarming statistics indicate that 1 in 5 Americans at some point in their lives will suffer from a mental disorder⁹. Though many mental health professionals work within the private sector, strong evidence indicates that the public sector's responsibility will be focused more on the seriously and persistently mentally ill (SPMI): The growing number of the homeless and those in trouble with the law, and the frail elderly. Probably >10,000 people fall into the category of SPMI¹⁰. These populations are considered to be difficult to work with at best. It is not surprising therefore that attracting qualified compassionate staff to provide the proper services continues to be a major challenge.

In Hawaii, lack of adequate training and education of staff have been cited in both external and internal reviews to be among the problems of our mental health system in general and HSH in particular^{6,11,12}. There is a need not only to recruit, but also to retain qualified and prepared staff.

The problem with the shortage of psychiatric nursing personnel is well documented^{13,14,15,16}. Nurses represent the largest group of the professional core providing mental health care in the country and the largest group practicing in state mental hospitals. In 1984, 31% of all employed psychi-

atric nurses were working in public mental hospitals (nurses, N=14,873, psychiatrists, N=3,665, social workers, N=3,935, psychologists, N=1,461). In 1987 in the U.S., there were slightly more than 50,000 professional psychiatric nurses¹⁷. Kramer projected a need to double this figure by 1990 if each patient in need of psychiatric services was to receive 6 hours of psychiatric nursing care a year¹⁴.

Because of the current and projected shortage of nurses, aggressive efforts to attract nurses into the field of mental health need to occur. At the same time, preparation of the nursing staff now employed at HSH is necessary so that staff can assume the roles and functions dictated by changing trends.

Fox, speaking at the Western Interstate Commission for Higher Education (WICHE) workshop on "The Changing Roles of Nurses in State Hospitals", emphasized the need for collaboration between universities and mental health systems¹⁷. She encouraged working together in mutual support, since both university schools and public mental health systems have difficulty with the recruitment of nurses. She suggested that nurses who want degrees could be attracted to state hospitals if established programs and rewards for obtaining educational degrees were available in situ. Faculty also need research facilities, support and access to clinical nursing staff to identify and discuss appropriate research questions.

"Staff will respond positively to being involved in research and they will want to work in a facility where something is happening in nursing. The state hospital becomes a vehicle for professional advancement and a supplier of students. The university can be used to enhance the commitment of employees to the state hospital by enriching the work experience and providing educational programs for advancement"¹⁶.

R & R at HSH

A Recruitment and Retention (R&R) project that addressed the education, training and recruitment needs of nursing staff at HSH was developed by faculty members of the University of Hawaii's SoN to assist in correcting reported deficiencies within the nursing-care delivery system. The Department of Health Behavioral Health Administration funded the 3-pronged project which focused on: a) Advanced education for nursing staff; b) consultation; and, c) continuing education courses for staff. This project was initiated in September, 1990.

The goal

The overall goal is to improve the quality of nursing care provided to the seriously and persistently mentally ill patients at Hawaii State Hospital by creating a learning

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School of Nursing
University of Hawaii

community within the hospital setting.

"Learning communities" are a result of deliberate restructuring of the nursing curriculum so that students are actively engaged in an academic relationship with other students and with faculty over a longer period of time than is possible in the usual traditional courses¹⁸. Other characteristics of learning communities include strategies to maximize student-centered learning, a sense of family environment, commitment to lifelong learning, and a greater level of personal interaction between students and faculty. The need to be creative in choosing teaching strategies that enhance different learning styles is well documented in the teaching and learning literature^{18,19,20,21}.

Advanced education for nursing staff

The first component of the project provides for nursing staff to continue their formal education within the University of Hawaii system. Employed nurses return to school to complete baccalaureate and master degrees in nursing, working reduced hours and receiving full pay. Nursing staff have enrolled for the first time in general education courses at community colleges with tuition paid by the grant. A payback clause has been formulated which expects 2 years of continual employment for each year of academic support.

Fifty of the nursing staff at HSH have been involved in this component. Three have completed their degrees and currently 20 are enrolled in University classes.

Nurse specialists consultation/clinical

The second prong provides 5 Clinical Nurse Specialists (CNS) who have joint appointments at the SoN. They provide services 80% of their time to selected in-patient units at HSH. Role-modeling of clinical skills and expertise in psychiatric nursing is the major focus of this group. In addition, 4 other CNS provide weekly consultation services to the staff at HSH. Two of these nurses are also Advanced Nurse Practitioners who focus on the medical services provided to the patients at HSH.

These nurse specialists work closely with the Nurse Executive Group to develop the foundation of practice of psychiatric nursing for HSH. The CNS participate in Quality Management, Policies and Procedures, and Peer Review; these are standing nursing committees that work on operationalizing the Standards of Psychiatric Nursing for practice at HSH. They also participate in hospital interdisciplinary committees.

The CNS also work with the nursing

staff on the hospital units to integrate and adapt the materials developed by working committees.

Continuing education

The final prong consists of education classes for nursing staff at HSH. Courses have been developed to meet the determined needs of the nursing staff. The CNS develop and teach courses in pharmacology, leadership and management, contemporary psychiatric nursing, group dynamics and the therapeutic use of self on the part of paramedical assistants. These courses are repeated several times a year making them available to all interested staff (22 courses have been offered to date).

(Continued on page 222) ➤



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An evaluation form was developed in consultation with staff development personnel for use in all classes offered at HSH.

A data base is maintained for analysis, feedback to instructors and critical evaluation by the department.

Purchase of educational computer-assisted instructions, videotapes, texts and journals enhance the continuing education offerings and support the principles of adult learning.

Coordination and administration of the project

The chief of the department of nursing at the HSH is on the faculty of the SoN and is assigned as the nurse manager to HSH for 80% of his or her time. As a nurse-leader, the chief guides the development of a nursing philosophy needed to build the morale of the nursing team and establish a therapeutic milieu. He or she is responsible for planning, organizing, and implementing all the nursing activities at the Hospital. The chief provides leadership in developing policy and procedures, standards of care and quality assurance indicators. He or she meets and reports to the Administration at HSH and generates quarterly reports to the Department of Justice.

The mental health educator coordinator (MHEC), 50% Full Time Equivalent administrator/principal investigator is on the faculty of the School of Nursing. She directs all aspects of the project in collaboration with the nursing administration at HSH. The MHEC recruits, advises and supports students throughout the course of their studies and acts as a resource for all staff at HSH interested in higher education. She coordinates the CNS group and provides a communication link between the hospital community and the Hawaii Council of Psychiatric/Mental Health Clinical Nurse Specialists, which acts as an advisory board to the project. The MHEC provides expertise and consultation to the staff development program at HSH.

The rationale for this position is based on the belief that application of acquired knowledge and skills is integrated into practice and results in delivery of care if the educator facilitates and supports the process in the actual work milieu.

Evaluation

A long-term study was designed to examine educational factors that have an impact on nursing recruitment in a public state hospital. Specifically, 4 questionnaires were constructed to measure outcome goals and criteria of the R&R project which relate to an environment conducive to: a) Learning from expert consultants (CNS); b) obtaining higher education; and, c) participating in continuing education.

Time 1 (April 1991) data were collected at 9 months into the project to provide information as a basis for continuation and modification of the project. This evaluation occurred 6 months after the DoJ settlement with the State of Hawaii and allowed time for the change process to be established.

Time 2 data were collected in November, 1992 and are being analyzed. The results will be ready for publication by the end of 1993.

This indeed is a time of great challenge and change for the staff of the entire HSH. The intent of the University of Hawaii and the Department of Health collaborative project is to assist the nursing staff in assuming leadership, executive and therapeutic roles, that are necessary for the successful transformation of Hawaii State Hospital into a fully accredited institution of care, teaching, learning and research for the seriously and persistently mentally ill.

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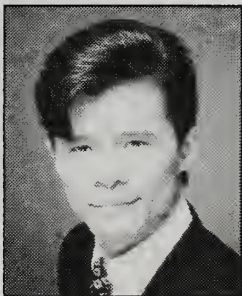
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Mike Okihiro's Retirement Roast

Randon notes therefrom

The Cannery Aug '92

Daughter, May: "Dad's been threatening to retire. Unconventional? He's definitely his own person. When Straub had it's annual formal dance, Dad wore his aloha attire."

"In a letter to the editor, he proposed a golf course on the Kapaa landfill. 'What can be more lovely than a golf course on the site of an old garbage dump?' 'The Okihiro Syndrome or apraxia of descending golf stroke,' the article appeared in the *Golf Digest* and in the *Hawaii Medical Journal*."

Daughter, Michele: "Dad has said when he dies there will be no inheritance. He has left us with the value of our education."

Mel Yee: "Mike's favorite expression: 'Ah...this patient...Waste time, this kinda case'."

Dick Kawata: "The last time I roasted Mike was at his 60th birthday, maybe 15 years ago. He's only 65? He looks older. Evelyn asked me to roast him. That would take over an hour, but to praise him a few seconds will do."

"I thought he retired a long time ago. I would call his office and he and Evelyn would be on a trip to Augusta, Pebble Beach, etc. all those juicy convention sites. Why did I think he retired? It dawned on me that it was his potbelly. No one has a potbelly like his. Retirement? Not by choice; all those unpaid bills. Can he make it on his social security? The AMA told him he has to retire. Lately he has been sticking those EEG wires up noses and in ears. Rumor is that 'He's kinda losing it'."

"You guys are wondering what he's gonna do: next week he's signing up for a crash course in Japanese. Then he will apply for a job as a tour-bus driver, 'Mina sama china man hatto' and Evelyn will distribute bento to the tourists. He will be going to the Ala Moana Shopping Center to 'talk story' with fellow retirees. Thursday afternoons he will hustle golf bets at the Mid-Pac Country Club. He'll have enough money."

"About hustle, this is a true story. Mike had a monthly meeting at Queen's lasting from 7 to 7:30 in the evening. He would call me up. I live in Nuuanu and Mike lives in Kaneohe. He would come over and ask my wife, 'How's your shoulder', 'How's the kids flu?'. He would ask me, 'How's your hemorrhoids?' Two or three weeks later we got a house-call bill from his office. I protested, and he answered, 'Well, I asked about the kids, that's a house-call.' Next time he came over, 'How's the kids' flu?' No response from my wife. 'How's your hemorrhoids?' I replied, 'None of your damn business.'"

"You know how Mike hates lawyers. He attended an AMA convention in New York

and found a brass rat in an antique store marked at \$500 that he bartered to \$100. When he left the store with the brass rat, the rats in the neighborhood followed him, just like the Pied Piper. He threw the brass rat into the East River and the rats all jumped in and drowned. Next day, he showed up at the antique shop and inquired, 'Have you got a brass lawyer?'"

"Seriously, I have a lot of respect for him. Man to man, friend to friend, he's a doctor's doctor. He's straightforward and honest. He always defended what he felt was right. He is a dedicated husband and father. He made sure that his kids attended the best schools."

Carl Kaizawa: "Mike is a no-nonsense, down-to-earth kind of guy. He loves to sing, especially in a crowd. When we attend the Rainbow games on the bus, Mike would sing the 'Star-Spangled Banner' from beginning to end. At the UH-Michigan game, after the UH band played the alma mater, Mike turned to the group, took off his jacket and proudly showed his Michigan T-shirt. Mike will be happy singing in his retirement."

Tom Kobara: "Mike had a reputation at Straub that he was an average neurologist, but had a terrible bedside manner. He would tell the patients, 'You know what you have? Piss-poor protoplasm'."

"Mike has a wicked 'stink eye'. In the Chapman Mix at Mid-Pac, poor Evelyn would take her 3-wood on the 17th hole and hit the ball OB and get a 'stink eye'."

Mel Yee: "Mike wanted me to get interested in sports, so he had me betting in football pools. All those Michigan games I bet on—if only I had bet against Michigan I'd be a rich man."

George Kimata of the DJ's: "Mike was a player-coach and he doesn't like to lose. We would round the bases like a coupla Kaneohe ice wagons. We played baseball together the past 12 to 13 years. Once Lynette Furukawa wanted to play on our team. Mike only laughed, Hah! Hah! Hah! So one day she got into the same elevator with Mike, her jugular pulsating and gave it to Mike. The players all start in the outfield. As they get older and can't see very well, they get to play first base, and finally when they really can't see, they get assigned as catchers. Our team has plenty of catchers."

Dave Sakuda of the rival Rascals: "Three things we all have in common: How we run the bases, how we all look stoned after 2 drinks, and I forgot what was the third. We played softball on rival teams for about 12 years—I'm on the other side. I had heard rumors that he was a compassionate physician, but as coach Mike showed no compassion and everyone got the shaft. Neurologists must be a special breed. Mike is very subtle."

"Don Ikeda says: 'Business is bad, you guys shouldn't beat them so much.' So back in 1986, the Rascals had won as usual. For the post-game dinner, we got to eat, not in the Gold, not even in the Silver, but in the Bronze room at the Wisteria for presumably a 7-course dinner. *Musubi* without even *ume*. The highlight was sliced ham, seafood was *namasu* with imitation abalone. We all have stories to tell, Mike, thanks for the memories."

Mel Yee: "The Okihiro Syndrome is the triad of Inspiration, Integrity, and Generosity."

Mike Okihiro: "Wassamata, you guys jealous? You doctors, I want you to promise me that

when I go, no CPR. Don't beat my chest and blow hot air into my mouth. Now I can take my time and smell the flowers. I'll see what comes along."

Re his career: "My father was a fisherman, his father was a fisherman and his father's father was a fisherman. But my father told me 'Don't be a fisherman'."

I love baseball. During the war we couldn't play baseball in Kaneohe, but Mid-Pac had a baseball team. That's why I went to Mid-Pac.

After graduation, I joined the army, but the war soon ended and I had the GI bill. We never heard of college in the country, but somehow I ended up at Michigan. Michigan Med School was great; I interned at Queens and from Queens I went to the Mayo Clinic, where Ralph Beddow trained. After finishing at Mayo, I came home, needed \$11,000 to start a practice. I went to the bank; the loan officer was a classmate I knew. He asked, 'You got any collateral?' I replied, 'Yeah, my four kids. So, no loan, no practice. That's how I got hired at Straub Clinic. You know, it's all been luck. I never planned things. They just happened.'"

Henry Yokoyama
News Editor



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Viewpoint from Maui News

by Russel T Stodd MD

Karl Marx has been dead for 110 years, and the failure of his economic philosophy was underlined for all time by the destruction of the Berlin Wall. Yet despite the obvious, the dream of central management in opposition to free enterprise lives on, right here in Hawaii.

In 1976 during the Ford administration, a comprehensive health planning law was enacted that was intended to monitor and direct major health expenditures. After several years, Congress recognized that the program was not effective, and federal funding was withdrawn. Many states discontinued the process, but in Hawaii the mechanism was continued in the state budget under the encompassing title, State Health Planning and Development Agency (SHPDA). Taxpayers of Hawaii are paying in many ways for this bad law that was deemed a failure by the State's own accounting agency, the Department of Accounting and General Services.

SHPDA has served to deny, delay, frustrate and even bankrupt well-intentioned, knowledgeable business and medical people seeking to provide medical facilities and/or equipment. To obtain a certificate of need (CON—the heart of the “planning” process), a potential builder/investor must document in detail what is intended, where it will be located, how it will be funded, whom it will serve, how it will be staffed, how it will impact other medical facilities, what income it will generate, etc., etc., *ad absurdum*. The completed document would rival the tax law.

After considerable expenditure of months of planning time, manpower and money, the applicant must appear before redundant councils and beg for approval. However, even if that approval is forthcoming, all the data must go before one person at the apex of the pyramid, and that person is the sole and final judge as to the granting of the certificate! This powerful individual at the summit is a gubernatorial appointee with no defined qualifications.

A superficial inspection of SHPDA's actions on Maui will reveal that a surgical center, an extended care facility, a Lahaina emergency unit, a small Lahaina hospital—all planned and funded by private parties—have been denied or discouraged by the SHPDA law. In addition, the action of the state agency in regard to denial of a privately funded

MRI facility was a shameful display of state manipulative power, under the guise of a CON choice. How preposterous! Is this America, land of the free, or someplace else?

At this time a CON application is pending for additional and vitally needed beds at Maui Memorial Hospital. Also, a necessary helipad for emergency evacuation of critical patients into and out of Maui Memorial Hospital must also go through the crazy quilt CON maze. One can only ask why we must endure the absurdities of this complex, obstructive law, which has obviously failed in both direction and function?

Recently, the local arm of this mech-

anism, a group of well-meaning citizens called the Tri-Isle Subarea Health Council, listened to testimony directed toward the need for a cancer therapy group unit in Wailuku. To their credit the local council endorsed the plan, but the real question is why should there be such a council at all? Does it make any sense that a qualified professional, willing to risk his own capital and eager to provide a vital service that the community needs, should have to prove to a clumsy, stratified, bureaucratic structure that he should be permitted to do so?

If Hawaii's citizens were confronted by a similar law to control and direct

(Continued) ➤

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where and what grocery outlets should be allowed (and to deny certain ones), or to dictate the sale of automobiles, or to decide what any other legitimate business enterprise should be allowed, if they were faced with such an abusive statute, we can be certain that the law would be struck down. Why therefore is medical business treated in this manner? One is inevitably led to the conclusion that the state Department of Health with its posturing gurus is determined to squash any sort of private competition.

This law must be discarded—not modified, not cleaned up, not corrected—simply discarded. Planning from the top fails, and there are truly thousands of irrefutable examples to establish that fact. The Berlin Wall came crashing down, remember?

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SALMONELLOSIS IN HAWAII: 1987 TO 1990

(Continued from page 214)

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Erratum:

In a recent Journal issue (52/6-June 1993) on p. 168, right hand column in the paragraph near the bottom beginning with "According to the author...", the sentence should read:
"Recently, the 1975 ogre of sudden death", instead of Sudden Infant Death. The author, Bob Dimler, of the article ADHD REvisited, brought this to our attention and added: "Although I will say I've seen a few 'hyperactive' babies. The sudden deaths have been of cardiac origin." Sorry, Bob, the error may too have been "whimsical" on our part.

The editor

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ONE RX FOR SOLO SURVIVAL (Continued from page 218)

educated and committed to accepting the changes in the way they practice.

Being more efficient in business will be one of the ways physicians can allow themselves the time to practice their skills. To accomplish this task, it will require skilled assessment of the one practice, and a commitment to accept new and innovative ideas. The reward could well be the achievement of that dream in the front year of medical school: Of being a healer and clinician, rather than a paper pusher!

(Mrs. McKenzie has been involved in health care for many years. Her emphasis and research in law school was in the medical-legal area. She has written and made speeches in local and international forums. An active member of the local medical community, Mrs. McKenzie is presently a marketing consultant.)

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CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and Lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic nng hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 16 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a \geq 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/– mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg oral dose, although this effect was not observed in a subsequent fertility study when the same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/m²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis); tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophils usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

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Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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Highlights of the HMA Council Meeting of July 9, 1993

Members present were: J Chang, A Don, F Holschuh, J Spangler, S Wallach, R Stodd, C Kam, C Lehman, B Shitamoto, M Cheng, HKW Chinn, R Kimura, M Shirasu, K Thorburn, C Kadooka, P Kim, H Percy, G Goto, J Lumeng, W Chang, J Kim, A Kunimoto, J McDonnell, W Dang; F Reppun, Editor, *HMJ*; Legal Counsel Vernon Woo; Auxiliary representative, E Don; HMA Staff: B Kendro, L Tong, J Asato, J Estioko, P Kawamoto and A Rogness (recording secretary).

The Council ordered that at the end of July, 80 members who have yet to pay their dues for 1993 be sent a certified letter informing them that they would be dropped from membership for non-payment of dues. In this respect, the treasurer reported revenues, basically from dues, are far behind projected budget figures.

President Jeanette Chang announced that a forum, by invitation only, was to be hosted by President or Mrs. Clinton to discuss health system reform on Tuesday, July 13, 1993, at a site to be determined; HMA has submitted names of 10 physi-

cians as possible attendees, as requested by the White House.

The HMA Auxiliary announced its willingness to support and work on the HMA's Distinguished Medical Reporting Awards program to assist with a number of tasks that might be assigned to its members.

HAMPAC reported its nomination of Mrs. Lillian Nishi for the Belle Chenault Award given by AMPAC to honor auxiliaries who have made a difference by their participation in political action.

The Council adopted and amended a mission statement for the new consortium for CME composed of the HMA and the UH School of Medicine.

It also ordered the appointment of a task force by the president to develop a policy on peer review for the HMA Investigative Committee in its dealings with non-member physicians and institutions.

Fred Holschuh
HMA Secretary



HMSA

HMSA has often come up with innovative projects. One of these is not new: The establishment of clinics, mostly in out-lying areas of the state, with salaried physicians in primary care facilities that are purchased or leased, staffed and fully equipped.

The other is new—introduced to physicians by a letter dated 1 March 1993 announcing HMSA's HealthPass.

The former has run into opposition on the part of physicians who feel that HMSA is competing with its own base of PARs (participating physicians) and particularly with "non-PARs", physicians who do not conform to the fee-for-service schedule of charges set by HMSA. The State Legislature has passed bills to restrict any expansion of such programs initiated by any mutual insurance company. Pressure is being put on the Governor to veto the legislation. [and he did/Ed.]

The pro side of the project claims that such clinics emulate what the federal government is already supporting—federally funded comprehensive primary care, comprehensive family health clinics such as Waianae Coast Comprehensive Health Clinic in Waianae, Kokua Kalihi Valley and some 5 or 6 others. These serve a need for medical and preventive care for certain populations that otherwise cannot or would not seek access to private physicians.

In a sense, HMSA's clinics perhaps foretell the future: "Managed care", which is now in the eye of both State and national focus.

The new HMSA proposal, Health Pass, is also food for thought. As usual, it is really not very new—it has been in existence for the past 3 years! HMSA states that "over 19,200 screenings have been provided...at our HealthPass facilities" during that period of time.

"HealthPass is a wellness program for adults which includes a health risk appraisal, standard screening tests and the evaluation and development of a Lifestyle Action Plan". Providers have to agree

and sign up to participate. Patients have to agree to pay half the cost.

We have a concern about the payment to the provider, not in terms of the dollar amount so much as what it does to the patient. Granted that it may bring the adult into the office, at least for a modicum of preventive care. But very few people ever consider seeing a doctor when they are well, and even if they do, they almost always have one or more complaints.

Even to evaluate a long-established patient's health status once a year takes at least 45 minutes to an hour, depending on the complexity of the case. A 15-minute quick history and cursory physical exam may very well give the patient a false sense of "all's well with me" at an out-of-pocket fee of \$26 (HMSA pays for the other \$26 for a total of \$52). We would not call that good practice.

On the other hand, it might well alert the examining doctor, if he or she is unusually perceptive and not overburdened, sleepy or tired, to something seriously wrong with that patient. We recall the old dictum: "Every doctor's office is a cancer detection clinic".

When one stops to marvel that in all the prior years of the existence of the insurance against medical illness and injury, no carrier would ever cover annual physicals for adults, this program by HMSA is truly a forward step. One of the reasons it was never covered previously was the fact that the annual physical could always lead to findings that would entail coverage by the insurance carrier for genuine diagnosis of unexpected and unanticipated illness, which would cost the carrier.

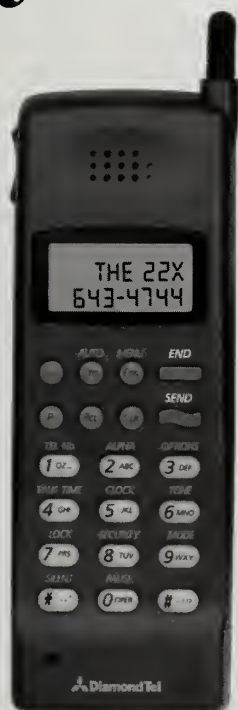
In essence then, HMSA's HealthPass is a welcome breach in that barrier, and it is indeed a step in the direction of preventive care—if people will be responsive and responsible!

J I Frederick Reppun MD

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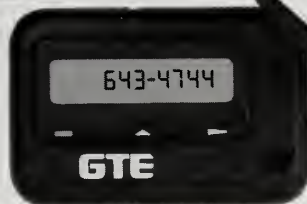
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Stroke and Traumatic Brain Injury (Ma'i Ulu) in Amerika Samoa

Gloriajean L Wallace PhD*

This paper discusses the annual incidence of stroke and traumatic brain injury (TBI) in American Samoa. Findings are based on data collected from the medical records at LBJ Tropical Medical Center in Amerika Samoa from June 1, 1989 to May 31, 1990. A review of these medical records revealed that stroke and TBI were prevalent among the residents of Amerika Samoa during the time period sampled. Health and cultural factors which contribute to the occurrence of stroke and TBI in Amerika Samoa and recommendations for further investigation and prevention of stroke and TBI in that country are discussed.

Neurological impairment may affect individuals from any racial or cultural group. However, the prevalence of specific causes of neurological impairment may vary across groups as a result of differences in genetic makeup, immunity factors, diet, living environment and cultural practices¹. These issues have been highlighted as they pertain to the multicultural population within the continental United States^{2,3}. However, there is a paucity of information addressing neurological impairment among American citizens from the multicultural community who reside in rural areas outside of the continental United States. One such group is the Amerika Samoans.

Amerika Samoa is a territory of the United States located in the Pacific Ocean approximately 2,000 miles southwest of Hawaii. The estimated population is 45,500⁴. Since World War II, the territory of Amerika Samoa has been greatly affected by Americanization, which some speculate could be a major contributor to increases in specific causes of neurological impairment among this population. These include stroke, which might be related to changes in diet, an increase in the prevalence of hypertension and diabetes^{5,6}; and traumatic brain injury (TBI) or *ma'i ulu* as it is called in that country⁷, related to increases in violent assaults⁸ which typically involve a blow to the head with a club or rock, and motor vehicle accidents⁹.

This study was conducted to obtain information about the occurrence of stroke and TBI among individuals seen at the LBJ Tropical Medical Center (LBJ) in Amerika Samoa over a one year period, from June 1, 1989 to May 31, 1990.

Methods

Data were compiled from the medical files at LBJ, which is the only major medical center serving the residents of the Amerika Samoan Islands. LBJ has recently installed a computer-based system for entry of patient information for all regis-

trants at the hospital. However, because complete data entries for the research period were not available at the time of data collection, it was not possible to obtain reliable information from a computer search. For this reason data for this study were compiled directly from the patient registration log books and the patient medical files for all inpatients seen at LBJ during the research period. Outpatient information was excluded from the review because the LBJ medical staff indicated that at their medical facility all individuals with a suspected diagnosis of stroke and TBI were admitted as inpatients. It was judged, therefore, that a review of inpatient log books would provide an accurate and direct means of identifying cases.

Inpatient Log Review

Patient medical chart numbers and corresponding medical intake diagnoses of stroke, TBI, or related diagnoses were compiled from the log books of 4 major hospital wards at LBJ: The intensive care, surgical, medical, and pediatrics units. Related diagnoses were included at this point in the search, in an effort to obtain a complete-as-possible list of likely stroke and TBI patients.

For the stroke group this included individuals with an initial intake diagnosis of stroke, cerebral vascular accident, hypertension, infarct, hemorrhage, TIA, dysphagia, ischemia, possible aspiration pneumonia, and questionable neurological status.

For the TBI group this included individuals with an initial intake diagnosis of traumatic brain injury, head injury, subdural hematoma, skull fracture, motor vehicle accident, cerebral concussion, scalp laceration, compound fracture, accidental fall, and scalp abrasion.

After the initial intake list was compiled, the same inpatient intake log books were independently reviewed by a research assistant to ensure that no possible stroke or TBI cases had been omitted. A total of 162 patients: 74 possible stroke cases and 92 possible TBI cases were identified in this manner from the log review.

Medical Chart Review

The medical charts contained information about the final definitive diagnosis as determined by each patient's physician. Charts for all 166 patients were reviewed to confirm the diagnosis of stroke or TBI. Patients with medical chart diagnoses other than stroke or TBI were eliminated from the roster at this point. The chart review was conducted by 2 teams comprised of the investigator and 3 research assistants. Each chart was reviewed by both members of a team as a self-check to minimize inaccuracies in data recording. For confirmed cases of stroke or TBI, information pertaining to birthdate, gender, ethnicity, cause (for TBI cases), presence of hemiplegia and survival post insult (for stroke cases) also was recorded.

Results

Stroke

Seventy-four individuals were seen at LBJ with a stroke-

(Continued on page 236) ►

* Currently: Department of Audiology and Speech Pathology University of Tennessee-Knoxville
Formerly on the faculty of the University of Hawaii and in research in Honolulu and in the South Pacific

Requests for reprints should be sent to: Gloriajean L Wallace, PhD, Department of Audiology and Speech Pathology, University of Tennessee, Room 457, S Stadium Hall, Knoxville, Tennessee, 37996-0740, phone: (615) 974-5019.

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related diagnosis from June 1, 1989 to May 31, 1990. This included 29 adults who were admitted with a stroke diagnosis and who survived to the point of discharge (mean age 65 years, $sd=8.15$). Forty-five adults (mean age 68, $sd=13.35$) were recorded as having stroke-related fatalities. The mean age in years for the fatalities was slightly greater than for the surviving cases.

Individuals from a variety of ethnic backgrounds are treated at LBJ (including Korean, Tongan, European, Japanese,

Chinese, Filipino, Micronesian, and Fijian). However, during the period of data collection for this study, only individuals of Samoan ancestry were identified as having incurred new episodes of stroke during the period of data collection for this study. Summary information for new stroke cases is presented in Table 1.

Of the stroke survivors, there were 23 males and 6 females. Eighty-six percent ($n=25$) of these survivors demonstrated observable motor impairment. This was true of 24 patients who were hemiplegic and 1 patient who had ataxic motor involvement, according to the medical records.

Stroke-related fatalities comprised approximately 24% ($n=45$) of the total deaths recorded at LBJ for that same time period ($N=186$). Stroke-related fatalities included 11 individuals who died of stroke-related problems after hospitalization and 34 who were dead on arrival at the hospital. According to the LBJ medical staff, diagnostic labels of stroke, CVA, history of hypertension, intracranial bleeding, cerebral hemorrhage, subarachnoid hemorrhage, arteriosclerotic vascular disease, and diabetes-related deaths are used in their medical center to indicate a stroke-related diagnosis. Patients with any of these diagnoses listed as a primary cause of death on the death certificate were considered to have died from stroke-related causes. The range in diagnostic labels used to indicate stroke, may be due to the fact that there is no neurologist on staff to assist with a final diagnosis.

TABLE 1
New Stroke Cases Seen at LBJ Tropical Medical Center From June 1, 1989, May 31, 1990

	CVA Fatalities		CVA Survivors	
	No.	Mean Age in years	No.	Mean Age in years
Male	23	64 $sd=14.89$	23	65 $sd=8.31$
Female	22	72 $sd=10.43$	6	69 $sd=7.34$
Total Male & Female	45	67.53 $sd=13.35$	29	65 $sd=8.15$

TABLE 2
New Surviving Adult Cases of Traumatic Brain Injury (TBI) Seen at LBJ Tropical Medical Center From June 1, 1989 to May 31, 1990

	CAUSES				
	Violent Assaults	Motor Vehicle Accidents	Accidental Falls	Misc. Accidents	All Causes
Male	24	11	6	—	41
Female	—	2	1	1	4
All Cases	24	13	7	1	45
Mean Age in Years for all Cases	30 $sd=8.77$	25 $sd=5.54$	42 $sd=16.11$	54 $sd=0.00$	31 $sd=11.22$

Traumatic Brain Injury

According to information provided in the log book, 92 individuals were suspected of having incurred TBI from June 1, 1989 to May 31, 1990. Review of medical charts confirmed that 76 of the original 92 were actual TBI cases. Sixty-nine of these were TBI survivors and 7 were TBI fatalities (6 adults and 1 child). Forty-five of the surviving individuals were adults ranging in age from 19 to 70 (mean age=31 years, $sd=11.22$) and 24 were children ranging in age from 6 months to 18 years (mean age=8 years, $sd=5.91$). Two percent of the adult TBI survivors and less than 1% of the pediatric TBI survivors were of non-Samoan ancestry. Ethnic backgrounds for these non-Samoan cases were Korean ($n=7$), Chinese ($n=1$), Filipino ($n=1$), and Tongan ($n=1$). Summary information for adult and pediatric TBI survivors is presented in Table 2 and 3.

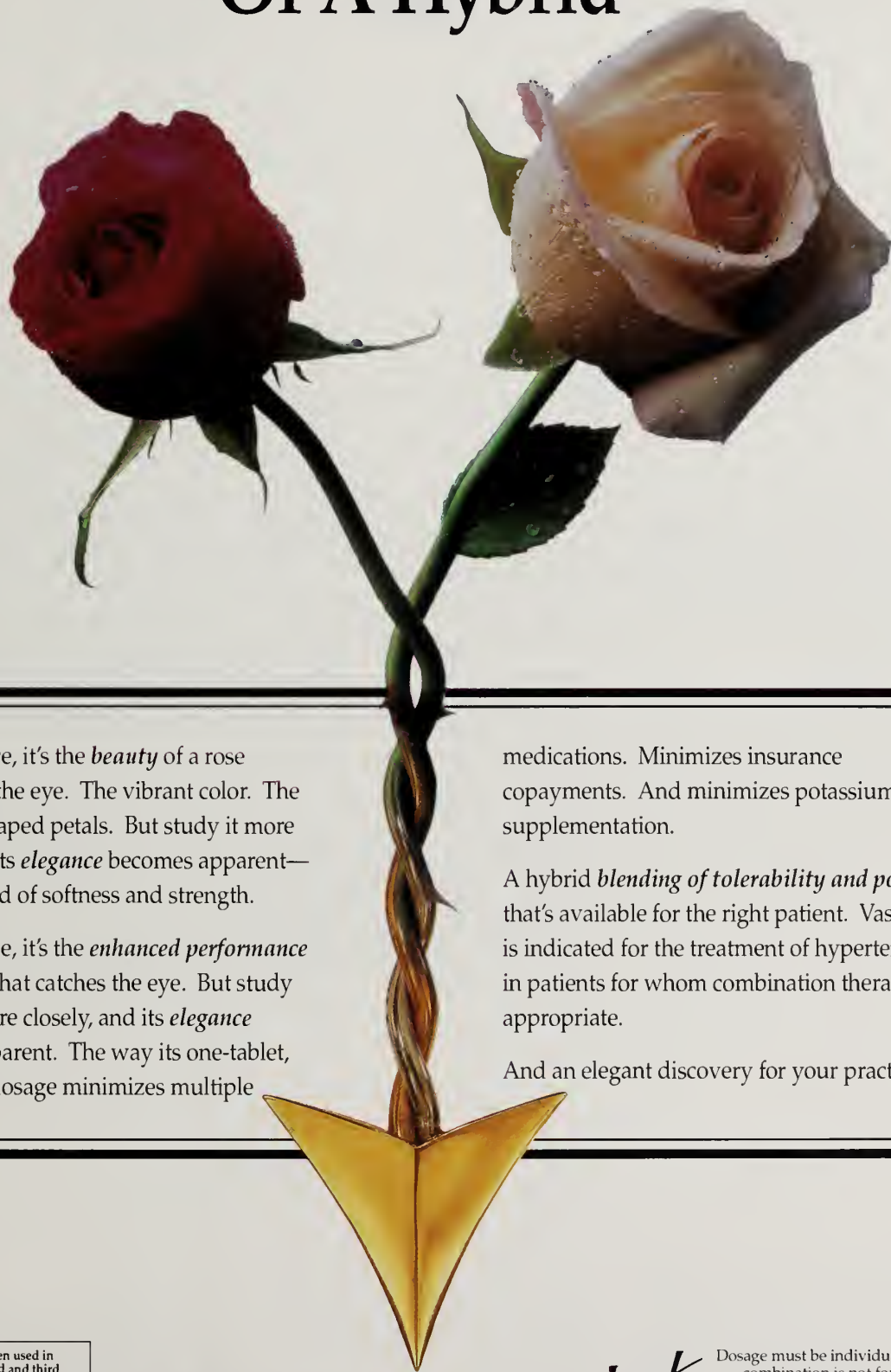
In the adult population, violent assaults and motor vehicle accidents were the most commonly listed causes of TBI, accounting for 82% of all cases. Accidental falls and miscellaneous accidents (hit by a ceiling fan) were reported to be causal factors in 18% of the adult TBI cases.

The most common causes of TBI in the pediatric population were accidental falls and motor vehicle accidents, which accounted for 79% of all reported cases. Violent assaults, sports-related accidents (rugby) and miscellaneous accidents (struck on the head with a hammer) were the cause of TBI in 21% of the pediatric TBI cases.

TABLE 3
New Surviving Cases of Pediatric Traumatic Brain Injury (TBI) Cases Seen At LBJ Tropical Medical Center From June 1, 1989 to May 31, 1990

	CAUSES					
	Violent Assaults	Motor Vehicle Accidents	Accidental Falls	Sports Related Accidents	Misc. Accidents	All Causes
Male	3	4	4	1	1	13
Female	—	5	6	—	—	11
All Cases	3	9	10	1	1	24
Mean Age in Years for all Cases	17 $sd=.58$	6 $sd=3.77$	6 $sd=5.99$	15 $sd=0.00$	6 $sd=0.00$	8 $sd=5.91$

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(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC (enalapril maleate-hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: General, Enalapril Maleate, Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, Drug Interactions, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 0.3 mL to 0.5 mL and/or measures necessary to ensure a patent airway, should be promptly provided. (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Enalapril Maleate and Hydrochlorothiazide).

Pregnancy, Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality, below.)

Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no

10
mg

25
mg

alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide, Teratogenic Effects: Reproduction studies in the rabbit, mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-liter study in rats at doses of 1-5 mg/kg/day (approximately 1-2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Neonatal Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: General, Enalapril Maleate, Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors including enalapril may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See Drug Interactions.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hyperkalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hyperkalemia. Hyperkalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see Drug Interactions, Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the

treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the postmyopathic patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium, this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients, Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: Enalapril Maleate, Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium. **Hydrochlorothiazide:** When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. Thiazides may be administered two to four hours before the resin when the two drugs are used concomitantly.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes of chromosomal aberrations in an *in vitro* mouse

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bone marrow assay.

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenetic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy, Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Enalapril and enalapril are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: **Body As A Whole:** Syncope, chest pain, abdominal pain; **Cardiovascular:** Orthostatic hypotension, palpitation, tachycardia; **Digestive:** Vomiting, dyspepsia, constipation, flatulence, dry mouth; **Nervous/psychiatric:** Insomnia, nervousness, paresthesia, somnolence, vertigo; **Skin:** Pruritus, rash; **Other:** Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS).

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS).

Cough: See PRECAUTIONS, Cough.

Clinical Laboratory Test Findings: Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS).

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate: Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: **Body As A Whole:** Anaphylactoid reactions (see PRECAUTIONS, Hemodialysis Patients); **Cardiovascular:** Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension, angina pectoris, **Digestive:** Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; **Hematologic:** Rare cases of neutropenia, thrombocytopenia and bone marrow depression, a few cases of hemolysis in patients with G-6-PD deficiency have been reported in which a causal relationship to enalapril cannot be excluded; **Nervous System/Psychiatric:** Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dyesthesia); **Urogenital:** Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecostasia; **Respiratory:** Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; **Skin:** Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, alopecia, flushing, photosensitivity; **Special Senses:** Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

Hydrochlorothiazide: **Body as a Whole:** Weakness; **Digestive:** Pancreatitis, jaundice (intrahepatic cholestatic jaundice), saladenitis, cramping, gastric irritation, anorexia; **Hematologic:** Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; **Hypersensitivity:** Purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions, **Musculoskeletal:** Muscle spasms; **Nervous System/Psychiatric:** Restlessness; **Renal:** Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); **Skin:** Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; **Special Senses:** Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

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Stroke

The number of individuals identified as having new strokes over the period examined was large, as expected, given the prevalence of specific health risk factors (hypertension and diabetes) for stroke in Amerika Samoa. Obtained figures for the annual incidence of stroke in Amerika Samoa were comparable to the annual incidence reported in the United States. During 1989 to 1990, the total population of Amerika Samoan residents age 55 years and above was 3,371⁴. Two percent of those individuals (N=74) were reported to have incurred stroke. Likewise, of the estimated 1989 U.S. population of 248 million, approximately 2 (N=500,000) of those individuals were reported to have incurred stroke¹⁰. During this same time period, stroke mortality in Amerika Samoa was 1% (N=55) of the population of individuals age 55 and above, whereas stroke mortality in the United States was less than 1% (N=147,470)¹⁰. The higher stroke mortality in Amerika Samoa may, in part, be related to available primary health-care options for treatment of stroke in Amerika Samoa as compared to that in the United States.

The local population in Amerika Samoa consider stroke to be distinctly different from traditional Samoan illnesses. Stroke is, in fact, referred to as a *palangi* or stranger illness, meaning an illness brought to their population from those of non-Samoan ancestry. This may account for why there is no word in the indigenous Samoan language for stroke.

Stroke is, for the most part, a health problem of the aging. Since the elder Samoan people are more likely to have limited exposure to and proficiency with the English language, it is likely that there is an underreporting of stroke by this population who could have little knowledge of this illness, and perhaps because there is no word to describe stroke when presenting symptomology to their physicians.

An additional point is that although hospital costs average only \$5 a day for residents of Amerika Samoa, this amount might not be affordable for many in this country. Thus, many stroke patients might opt to remain at home after a stroke, and might not be accounted for in the LBJ records. For these reasons the actual occurrence of stroke could be higher than is reported here. Further ethnographic investigation into this issue is needed for a more complete understanding of stroke and how stroke is perceived and managed within the context of traditional Amerika Samoa culture, which has its own system of traditional healing or *Fo* medicine¹¹.

The presence of neurological insult due to stroke is difficult to diagnose in instances where there is no substantial motor involvement. This is particularly true when the diagnosis is being made in a rural community such as Amerika Samoa where there is no neurologist available nor is there medical technology (for example, computerized tomography, magnetic resonance imaging, and angiography) to assist internists in confirming a suspected diagnosis of stroke. In such instances physicians can rely on observations regarding the patient's speech, language and cognitive performance, which could complement clinical medical findings and assist the physician in confirming the presence of neurological impairment and stroke.

Additionally, in Amerika Samoa only a small percent of the physicians have Samoan as their first language. Limited Samoan language proficiency makes it difficult, if not impossible, to identify aberrations in communication which might otherwise facilitate the medical decision regarding diagnosis.

In the present study the majority of stroke patients (86%) were described as having observable motoric involvement. Since so few nonmotor-impaired individuals were identified,

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patients presenting with *silent strokes* (aberration of communication after stroke in the absence of frank motor involvement) could have been underreported because of the likely difficulty in providing a definite diagnosis in such cases. At present there is no regular staff speech-language pathologist at LBJ who is fluent in Samoan and available to assist with screening neurologically based communication impairment where such problems are suspected. Future inclusion of a speech-language pathologist on the medical team could provide physicians with useful information to facilitate diagnosis where aberrations in communication skills provide an important clue regarding the presence of neurological impairment.

An additional point regarding the number of identified cases of stroke is the fact that identified cases were taken from the inpatient registry only. However, because the LBJ Hospital staff reported that all stroke patients are registered as inpatients, it is unlikely that additional individuals would have been identified had the outpatient roster been inventoried.

TBI

Although proportionately less than cases of stroke, a significant number of both adults and children were identified as having incurred new episodes of TBI severe enough to warrant hospitalization. The obtained annual incidence of TBI in Amerika Samoa was somewhat lower than the incidence of TBI in the U.S. Out of an extrapolated total Amerika Samoan population of 46,150⁴ during 1989-90, less than 1% (N=76) incurred TBI. In the same time period, the annual incidence of TBI in the U.S. was 500,000, or 2% of the total U.S. population of approximately 248 million¹². A larger number of individuals (with milder forms of head injury) might have been identified in the annual incidence of TBI in Amerika Samoa had the investigator included outpatients.

Violent assault was a primary causal factor for TBI in Amerika Samoa. This supports previous observations of extreme, violent aggression among the young male population in Amerika Samoa¹³⁻¹⁸. This aggression has been most consistently attributed to stringent discipline in Amerika Samoa, which then generates high levels of anger with no outlet for expression. While social constraints in this culture help to keep in check internal feelings of anger and hostility, display of anger is acceptable when one is presented with a challenge to status or self-esteem, which is considered to be a severe affront. Some have speculated that the effect of social control on self-constraint might be dampened in the young male population, who have a somewhat ambiguous social status. This might account for the high rate of violent assaults in this age group.

Another observation relating to violent assaults and TBI in Amerika Samoa was the repeated report by research informants that current-day brawls are almost always characterized by a conscious effort on the part of the fighters to locate a weapon suitable for executing a blow to the opponent's head. This could suggest a strong influence from traditional Samoan weaponry and warfare on current-day fighting methods (personal communication from the curator of Jean P. Haydon Museum and Director of the American Samoa Archives Office, Amerika Samoa, 1991).

The most frequently reported cause of TBI in the pediatric population was accidental falls. The second most common cause of TBI in this group was, as in the adult population, motor vehicle accidents. The main thoroughfare on Tutuila,

Amerika Samoa (where this study was conducted), is bordered by the ocean and circles a good portion of the island. The posted speed limit for this road is 35 mph. Although not posted, the speed for vehicles traveling on roads cutting across the mountainous regions of Tutuila is generally much slower.

In Amerika Samoa many people do not own motor vehicles. Those who do, often purchase pick-up trucks rather than cars, so that the vehicle can be maximally utilized for pooling rides among family members and friends and for other purposes such as carrying building supplies. Although Amerika Samoa has a seatbelt law (American Samoa Government Public Law 20-79), passengers who ride unprotected in the back of pick-up trucks, as long as their bodies do not extend beyond the interior portion of the vehicle (including the floor or the box, bed or frame of the pickup exterior) are not included (Section 22.0704)¹⁹. This could account for many of the motor vehicle-related traumatic brain injuries in both the adult and pediatric populations.

According to the Chief of Police in Amerika Samoa, the high rate of occurrence of motor vehicle accidents in Amerika Samoa also could be related to the existing motor vehicle safety law, not strongly enforced until 1991. Increased attention to the importance of seatbelt use in preventing accidents is evidenced through the numerous public service announcements recently developed for radio, and 2 large motor-vehicle safety reminder signs placed in the downtown market area as of 1991. These measures will help to reduce the occurrence of head injuries secondary to motor-vehicle accidents in the future.

It is uncertain whether more stringent safety laws for passengers of pick-up trucks would further reduce fatalities and traumatic brain injuries in this country where such a large number of people depend on riding in the rear section of pick-up trucks for their transportation. However, investigation into creative solutions to reduce injuries related to pick-up truck accidents is clearly warranted.

Conclusions

Follow-up investigation over a longer time-span is needed to explore the trend in annual incidence of stroke and TBI in Amerika Samoa. Data presented here indicates there is a sizable number of new, yearly cases of stroke and TBI in Amerika Samoa. Special attention needs to be given to prevention of stroke and especially TBI, which appears to pose a significant health problem in Amerika Samoa. The establishment of local chapters of the American Heart Association and the National Head Injury Foundation may be a useful first step toward community education and the dissemination of information about the prevention of stroke and TBI.

In addition, further research is needed to explore the management of rehabilitation in stroke and TBI individuals in Amerika Samoa. In the continental U.S., it has been reported that more than half of all survivors of stroke and TBI are unable to fully return to their premorbid life-style because of residual impairments in cognition, language, motor speech, feeding/swallowing, ambulation, and emotional adjustment. Rehabilitation has been shown to facilitate re-entry into the community and reintegration by survivors of stroke and TBI. However financial, logistical and cultural variables limit the availability and utilization of rehabilitation services among certain segments of our population; notably the poor, those from the multicultural community and those residing in rural areas.

(Continued on page 240) ►




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We, in a follow-up of this study, conducted a field interview survey in Amerika Samoa to obtain information about rehabilitation needs for residents who were identified as having incurred stroke²¹ and TBI²². Results were that the Physical Therapy Department at LBJ was effective in making its services available to all stroke patients who had difficulty with ambulation or use of the extremities. No physical therapy was provided for the reported cases of TBI. An additional finding was that neither direct nor indirect speech-language pathology services were available for stroke or TBI patients with impairments in communication and feeding/swallowing.

Limitations of funding challenge the expansion of health care for residents of Amerika Samoa, particularly the handicapped. However, greater attention needs to be given to the development of comprehensive rehabilitation services, including speech-language pathology services, for this underserved population. This must be done in order to provide the opportunity for an acceptable quality of life for all residents of Amerika Samoa, including those with stroke and TBI.

ACKNOWLEDGEMENTS

The author would like to thank Dr. Saleapaga, Medical Director of the LBJ Tropical Medical Center in Amerika Samoa; Dr. Mik McCudden, Director of Public Health at the LBJ Tropical Medical Center; the LBJ Medical Records Department staff; and the LBJ nursing staff for their assistance with this research. This research was supported in part by a University of Tennessee-Knoxville (UT-K) Research Development Award, a UT-K Social Science Research Fellow Award, and a fellowship award from the World Rehabilitation Fund, under a grant from the National Institute of Disability and Rehabilitation Research, U.S. Department of Education, Washington, DC 20202-2646.

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

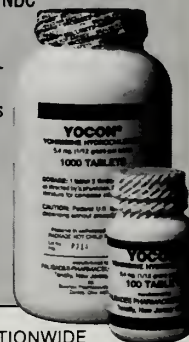
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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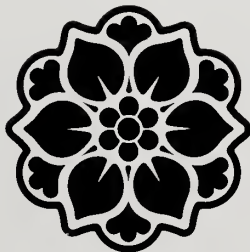
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Blood Lead Levels Among Children in Hawaii

Gertraud Maskarinec MD, MPH*

The objectives of this study were to estimate blood lead levels of children under 6 years of age in the State of Hawaii, to identify high-risk populations, and to decide what kind of blood lead screening program is needed in Hawaii. Children from Oahu and Maui were recruited in medical care facilities and 6 preschools. Informed consent for a blood lead test was obtained from the parents. A questionnaire was administered whenever possible; participation/response rates were quite low, varying between 15% and 50%.

The mean blood lead level for the 389 study participants was 4.5µg/dL. Twelve children (3% of children tested) had a level above 9µg/dL. No child was found to have a level above 14µg/dL. Blood lead levels varied by age, geographic area, occupational factors, laboratory that performed the analysis, and type of phlebotomy (capillary versus venous) but not by sex, ethnicity or age of home. Follow-up investigations in the 12 homes of the children with levels above 9µg/dL were performed and in 3 homes a possible source of lead exposure was found.

Introduction

Despite the low participation rate, the study appears to be fairly representative of Hawaii's children since it included children from different geographic areas and housing types, with varying socioeconomic and educational backgrounds. There is no reason to think that the true distribution of blood lead levels among children in Hawaii differs drastically from the results in this study.

Education of the public and alerting the physicians are needed to reach families whose children are at risk for lead exposure. Children exposed to any one risk factor (living in an old home with peeling paint, parents' occupational exposure to lead, water catchment system) should receive a blood lead test. Mandatory lead testing of all children in Hawaii would not be cost-effective and is not recommended.

Until recently, blood lead levels that did not cause symptoms of lead poisoning, namely anemia, abdominal pain, paralysis and encephalopathy, were considered safe. However, growing evidence indicates that low levels of blood lead have subtle adverse effects in children^{5,6}. Neurobehavioral effects are of special concern during the fetal period and the early years of life because the neurologic system develops rapidly during that time. Lead's neurotoxic effects at relatively low exposure levels include impaired mental or motor development, decreased intelligence, learning disabilities, impairment of visual-motor functioning, poor perceptual integration and poor memory, hyperactive behavior and alteration of hearing thresholds. The damage to the neurologic system caused by lead is considered irreversible.

Lead has no essential function in the human body. Studies among remote populations provide evidence that there is no "normal" blood lead level in the sense of a natural background level^{1,7}; human blood lead levels are caused entirely by the products of industry and the resulting dissemination of

lead into the environment. In 1970, a level of 60µg/dL was defined as "undue lead absorption." One year later this was lowered to 40µg/dL. In 1975, the Centers for Disease Control (CDC) changed the limit to 30µg/dL and in 1985 to 25µg/dL¹⁰. In October 1991, the CDC published a recommendation to lower the level of "undue lead absorption" to below 10µg/dL¹¹. Levels in the border zone of 10 to 14µg/dL should be rescreened and should trigger a community public health investigation. The steady lowering of the accepted threshold for lead's toxic effects can be interpreted as evidence that there is no intrinsic threshold for lead and thus presents a "continuum of toxicity."

Average blood lead levels in the United States decreased from 14.6 to 9.2 µg/dL from 1976 to 1980, and has possibly decreased since then¹¹. This change has been attributed to the reduction of organic lead additives in gasoline during the same time period. However, other possible sources for lead exposure remain: Lead-based paint, lead in soil, foods, drinking water, air, as well as occupational exposure.

The main source of exposure to lead among lead-poisoned children in urban areas is lead-based paint. Children may ingest lead directly from paint chips, but an important route of exposure is the normal mouthing of hands or objects such as toys, resulting in the ingestion of small amounts of lead-paint-contaminated house dust and soil. Children living in deteriorating housing built before 1950 are at high risk for excessive exposure to lead via this route. The lead content of paint used during that period varied; with some, particularly in earlier years, containing as much as 50% lead by dry weight. The 1987 Housing Act established an allowable level of not more than 0.5% for paint used in public and Indian housing and on Indian reservations.


The Federal Government has made lead abatement and the prevention of childhood lead poisoning a priority. The U.S. Department of Health and Human Services (DHHS) published a Strategic Plan for the Elimination of Childhood Lead Poisoning in February 1991¹². Several environmental organizations, such as the Environmental Defense Fund² and the Alliance to End Childhood Lead Poisoning, concentrate their efforts on this issue also.

The most recent data on blood lead levels available for the State of Hawaii come from a study on the Big Island (unpublished data) conducted jointly by the CDC and the Hawaii State Department of Health (DoH). In 1988, CDC-DoH investigated water catchment systems and offered testing for lead to families consuming drinking water from rainwater catchment. From the participating 93 children under age five, 12 (13%) had blood lead levels above 10µg/dL and 6 (6.5%) above 15µg/dL. The mean blood lead level was 6.4µg/dL. In 1973 a small study compared blood lead levels of children in Hawaii and New Jersey⁴. The mean blood lead level in Hawaii was 17µg/dL at the time. Other studies performed in the state used zinc protoporphyrin (ZPP) as a screening test which does not identify children with blood lead levels below 25µg/dL⁹. Nevertheless, the data provided evidence that very few children in Hawaii experienced severe lead toxicity.

Our present study was initiated when a committee within the DoH realized data on blood lead levels were lacking at a

(Continued on page 244) ►

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BLOOD LEAD LEVELS AMONG CHILDREN IN HAWAII (Continued from page 242)

time when new CDC recommendations to lower intervention levels for lead were imminent. The objectives of our study were to estimate blood lead levels of children under 6 years of age in Hawaii, to identify high-risk populations, and to decide what kind of blood lead screening program is needed in Hawaii.

Methods

Children from Oahu and Maui were included in the study and were recruited either in a medical facility or in a day-care center (Table 1). Budget constraints and logistical problems made it impossible to include the Big Island and Kauai. Blood samples were collected between March and August 1992. In the participating clinics, research assistants talked to parents of children <6-years old, preferably to those who were scheduled to have blood taken for other reasons. Some older children were included on parents' requests. After explaining the purpose of the study, the research assistant obtained written informed consent for the blood lead test and administered a short questionnaire. Blood was taken in the lab after the child had been given a health check by the doctor. Table 1 shows estimated acceptance rates. A high percentage of parents refused to have their child tested and another smaller percentage failed to take the child to the lab even though they had signed the consent form. Physicians at the Waianae Coast Comprehensive Health Center, at Maui Medical Group, and in private practice recruited their own patients for the study and no information on participation rate is available from these sources.

The preschools were selected to cover different areas on Oahu. Not all preschools that we approached were willing to participate; one organization refused because of legal concerns. In the cooperating schools, we sent a letter to the parents of the preschool children asking them to sign the consent form and to send it back to school. Depending on the school, between 15% and 30% of the parents consented. The highest acceptance rate was achieved in Kalihi's Headstart and Zero-to-Three Program where we had the opportunity to meet with some of the mothers and to explain the significance of high blood lead levels to them. The blood from the pre-schoolers was drawn at the school on a designated day.

The blood lead analysis were performed by 3 different laboratories. The choice of a particular lab for a sample was dictated by practical considerations. One of the labs (Kaulson) is located on the East Coast. Two are located in Hawaii (SmithKline and Diagnostic Laboratory Services) but these also send their samples to the Mainland for analysis. At this time no laboratory in Hawaii performs blood lead analysis routinely. All 3 labs participate in regular quality assurance programs. The measurement error for the atomic absorption spectrometry method is approximately $\pm 2\mu\text{g/dL}$. To avoid contamination, venous blood was drawn whenever possible; 237(61%) of all samples were venous samples. However, some of the clinics preferred to take capillary samples, and they were instructed on how to clean the finger appropriately.

Interviews were conducted over the phone in those families who had not been recruited by one of our research assistants. The questionnaire contained questions about the child's behavior and health, the child's home, risk factors for lead poisoning such as parents' occupation and hobbies, ceramic dishes, education and income level (Appendix). Test results were returned to the health care providers for children recruited in clinics and to the parents for children recruited in preschools. Parents of children with blood lead levels of $10\mu\text{g/dL}$ and above were contacted and offered a home visit to check for lead in paint and other potential sources. A commercial kit for instant environmental lead testing was used (Leadcheck™).

The zip code information was aggregated into larger geo-

graphic areas with the goal of calculating mean levels of blood lead from at least 10 samples per area. To get a rough idea in which areas sampling proportions were higher or lower than in the entire study, a sampling index was calculated. The number of

TABLE 1: Locations of Sample Collection and Participation Rate

	Location	Number Tested	Percent Participation	Mean blood Lead ($\mu\text{g/dL}$)
CLINICS	All	445	?	4.1
	DOH-Kauai	166	?	3.4
	Kaiser Moanalua	70	50%	4.7
	Kaiser Honolulu	67	25%	5.2
	Kapiolani	61	20%	4.8
	Waianae Coast	12	?	5.3
	Maui Medical	49	?	2.9
	Other	20	?	5.6
PRESCHOOLS	All	124	23%	4.0
	PTA (Kalihi)	52	30%	4.7
	Olivet Baptist	22	25%	3.5
	HCC-Waipahu	15	20%	3.2
	HCC-Kailua	17	20%	3.5
	HCC-Salt Lake	9	15%	2.0
	Kamehameha/Waimanalo	9	20%	5.6

FIGURE 1. DISTRIBUTION OF 569 BLOOD LEAD LEVELS IN CHILDREN

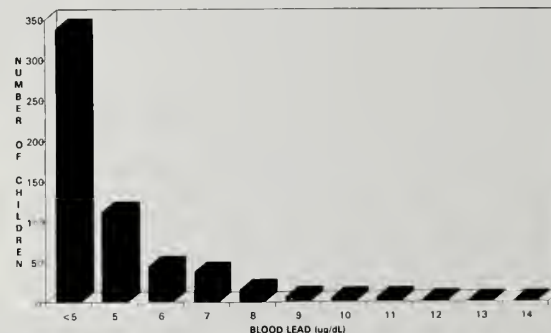


TABLE 2: Characteristics of Study Population

		Number	Percent	Census90
SEX	male	289	51	—
	female	280	49	—
AGE	<1 year	35	6	—
	1 year	119	21	—
	2 years	90	16	—
	3 years	117	21	—
	4 years	137	24	—
	>5 years	15	3	—
RESIDENCE	Oahu	353	62	—
	Kauai	166	29	—
	Maui	35	6	—
	Big Island	1	<1	—
ETHNICITY (n=334)	Hawaiian	105	31	—
	Mixed	83	25	—
	Samoan	35	10	—
	Filipino	24	7	—
	Caucasian	35	10	—
	Japanese	21	6	—
	Chinese	7	2	—
	Black	6	2	—
	Other	18	5	—
FAMILY INCOME (n=314)	<\$15,000	96	31	10
	\$15-30,000	92	29	21
	>\$30,000	126	40	69
EDUCATION OF PARENT (n=326)	<12 years	24	7	20
	High School	115	35	29
	College	149	46	44
	Graduates	38	12	7
AGE OF HOME (n=330)	<15 years	100	30	21
	15-30 years	125	38	52
	>30 years	105	32	27

tests performed per geographic area was divided by the number of births in 1991 for the same geographic area. The resulting figure for each area was divided by the overall ratio, ie 389 tests by 19,880 annual births. This index is greater than one if proportionately more children were tested in a particular area than across the State and less than one if proportionately fewer children were tested than across the State. The study made an effort to include many children from areas that were considered high-risk because of old housing, such as Waimanalo, Kalihi and Waianae.

All data were entered into a spreadsheet. The statistical analysis was performed with the help of SAS, using standard procedures for calculating prevalence rates, chi-squares, and T-tests.

Results

Altogether, 389 children were tested for lead. Characteristics of the study population are listed in Table 2. The mean blood lead level in this study was 4.5µg/dL with a standard error of 0.11. That means the population mean for children in Hawaii can be expected to lie between 4.3µg/dL and 4.7µg/dL, assum-

ing that the study participants are representative of the population. The overall distribution of blood lead levels (Figure 1) shows that over 50% of all lead levels were < 5µg/dL. Twelve children had a level above 9µg/dL (3% of all children tested). No child was found to have a level above 14µg/dL.

Figure 2 illustrates the distribution of blood lead levels by age. As expected, the younger children had a somewhat higher proportion of levels above 5µg/dL. The mean blood lead level differs significantly ($p=0.04$) among age groups. Infants under one year had the lowest mean level with 3.8µg/dL, whereas 1- and 2-year-old children had slightly higher mean levels (4.9µg/dL and 5.1µg/dL respectively). This difference is significant ($p=0.04$).

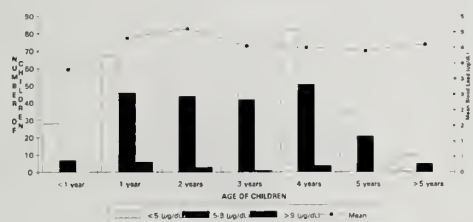
The sex of the child was not associated with the blood lead level; the mean was 4.6Jg/dL and 4.4g/dL for boys and girls respectively. Information on ethnicity was available in only 278 children. Among those, no statistically significant difference in lead levels was found (Figure 3). Filipino and Japanese children were underrepresented in the study.

Mean blood lead levels by geographic area (Table 3) range between 3.2µg/dL on Maui and 5.6µg/dL in Aiea. Considering the measurement error of the lab method, this range is quite narrow. The sampling index indicates areas with a high proportion of samples, especially Waimanalo, Kalihi, Manoa and Moiliili/McCully, whereas Pearl City, Salt Lake, Waianae Coast, Windward Oahu and the north shore were less well represented. The smaller the standard error of the mean for each area, the more stable the mean blood lead level for this area.

The mean blood lead levels differed significantly among the 3 laboratories: Kaulson 5.0µg/dL, SmithKline 4.5µg/dL, and Diagnostic Lab Services 3.4µg/dL. The mean blood lead level for capillary samples was 4.9µg/dL which statistically is significantly higher than the mean of 4.2µg/dL for venous samples. The

(Continued) ►

FIGURE 2. DISTRIBUTION OF BLOOD LEAD LEVELS BY AGE



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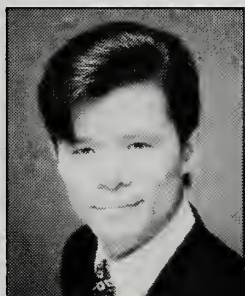
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7.24%	4.20%
APR	APR

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BLOOD LEAD LEVELS AMONG CHILDREN IN HAWAII (Continued from page 245)

difference between the labs persists after controlling for age and type of phlebotomy (venous versus capillary). Figure 4 illustrates the complex relationship between age of child, type of phlebotomy, and laboratory.

Of the 389 in the study, 284 (73%) included a parental interview. The mean blood level of those interviewed was significantly higher than in those not interviewed (4.7 $\mu\text{g}/\text{dL}$ versus 4.0 $\mu\text{g}/\text{dL}$, $p < 0.004$). Of all children whose parents were interviewed, only 3 (2.1%) had ever received a lead test before. Of 187 (67%) children, their health was described as excellent or very good. The blood lead levels did not differ significantly based on health status nor by number of symptoms experienced during the previous 3 months. Table 4 lists mean blood lead levels by risk factor. The differences between the means are minute for the most part and only 3 are statistically significant: Putting fingers into mouth, welding as father's occupation, and mother's occupational status as homemaker. Of the 178 children living in homes less than 30 years old, the mean blood lead was 4.6 $\mu\text{g}/\text{dL}$, whereas in the 95 children in homes older than 30 years, the level was 4.99. That difference is not statistically significant.

The parents of the 12 children (all in different families) with levels above 9 $\mu\text{g}/\text{dL}$ were offered follow-up investigations. Five families agreed to an investigation, 5 families could not be contacted, 1 family refused a visit and 1 home had already been checked for lead by the Housing Authority and no lead had been found. In 2 of the 5 homes visited, no leaded paint or other potential source for lead could be identified in or around the home. The babysitter's house could have been a source of lead for 1 of those 2 children. In one home, older layers of paint in the kitchen and outside the house contained lead. Most of it was in a satisfactory state and the parents were advised to take care of the few flaking spots. In another home the paint was new; however, the father, who was occupationally exposed to lead, brought home metal pieces containing lead and the children had actually played with them.

The child with the highest level (14 $\mu\text{g}/\text{dL}$) lived in a modern apartment building with latex-based paint. However, several old buildings had been torn down in the neighborhood and dust could have blown into the area where the child played outside. Since some tests had been done on capillary samples, a repeat test was recommended to these 12 families. So far, no family has taken the children to the lab for retesting.

Discussion

The mean blood lead level of 4.5 $\mu\text{g}/\text{dL}$ and the 3% proportion of levels above 10 $\mu\text{g}/\text{dL}$ in the 389 children tested is very low in comparison to the Big Island roof catchment study in 1988 and as the national studies. The trend of decreasing levels has been observed across the nation and is attributed to the introduction of unleaded gasoline¹¹. We would like to know how many children in Hawaii might have levels above 14 $\mu\text{g}/\text{dL}$ despite the fact that no child with such a level was found in the study. Assuming that the 389 study participants are representative of all children in Hawaii, the upper limit for a 95% confidence interval for the proportion of children with levels above 14 $\mu\text{g}/\text{dL}$ can statistically be calculated as 0.0077. That means a 95% probability that not more than 0.77% of all children have blood lead levels above 14 $\mu\text{g}/\text{dL}$. In approximately 100,000 children < 6-years old, as many as 770 children in Hawaii could have levels above 14 $\mu\text{g}/\text{dL}$. Such a number is considerably lower than that estimated by the Agency of Toxic Substances and Disease Registry¹³. In 1988, they estimated that 31% of all children in Honolulu might have levels above 9 $\mu\text{g}/\text{dL}$ and that 9% had levels above 14 $\mu\text{g}/\text{dL}$.

The major shortcoming in our study was the enormous rate of refusal to undergo a blood lead test. Many parents had never heard about lead. Many of those who had heard about it believed that they

did not have a problem. However, the strongest factor in deciding whether or not to participate seemed to be the reluctance of the parent (even among health and public health workers) to have a child undergo a phlebotomy. On the other hand, the children themselves were mostly cooperative and showed few signs of fear when they underwent phlebotomy at the preschools.

If the 389 samples are representative of children in Hawaii, this study shows that lead is not a major health problem for children in the state. There are some indications that most population groups were represented in our study. The proportion of Hawaiians/Part Hawaiians in the study is approximately equal to their proportion among recent births. Recent immigrants were included through the Headstart and Zero-to-Three program in Kalihi. By comparing the income structure of the study families to that in the 1990 census (Table 1), it can be interpreted that a greater proportion of low-income families were included in our study. Educational attainment was slightly higher among study participants than in the general population. The age of the home, as far as it was known, was approximately representative of homes in general. It may still be possible that those children whose parents did not accept a lead test had radically different lead levels than our participants.

Certain geographic areas are under-represented in our study. For the island of Kauai, there is no known reason to indicate that lead

FIGURE 3. DISTRIBUTION OF 334 BLOOD LEAD LEVELS IN CHILDREN BY ETHNIC GROUP

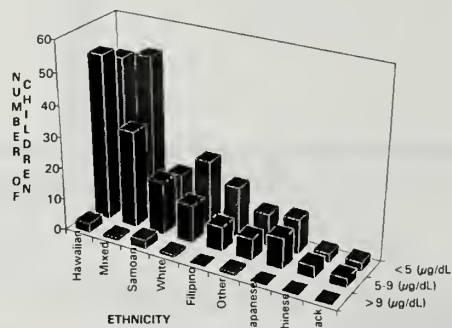


TABLE 3: Mean Blood Lead Levels by Geographic Area

Island	Area	Number Tested	Mean Blood Lead ($\mu\text{g}/\text{dL}$)	Standard Error	Sampling Index*
OAHU	Aiea	11	5.6	1.02	0.6
	Ala Moana/Waikiki	13	5.3	0.71	1.0
	Oowtown	13	4.8	0.38	1.7
	East Honolulu	23	4.1	0.22	0.9
	Ewa Beach	23	3.9	0.33	0.7
	Kalihi	76	4.9	0.23	2.6
	Manoa	22	4.6	0.36	1.8
	Moiiliili/McCully	19	4.6	0.63	1.6
	Nuuanu	25	5.0	0.35	1.2
	Pearl City	10	4.1	0.53	0.6
	Salt Lake	18	3.6	0.44	0.4
	Wahiawa/Mililani/North Shore	18	4.8	0.54	0.3
	Waianae	17	5.5	0.59	0.6
	Waimanalo	22	4.4	0.41	3.4
	Waipahu	19	4.8	0.69	0.6
	Windward	19	4.5	0.56	0.4
KAUAI	East Kauai	84	3.2	0.19	5.9
	West Kauai	68	3.4	0.23	7.8
	North Kauai	14	3.8	0.55	2.8
MAUI	All areas	49	2.9	0.29	1.2
UNKNOWN/OTHER		6	4.2	0.83	n.a.
TOTAL		569	4.1	0.09	1.0

* Index >1 indicates a higher than average number of children were tested.

levels would be drastically different from the rest of the state. For the island of Hawaii, it is known that some water catchment systems contain lead. Data from the 1988 CDC-DoH study showed a mean blood lead level in children under 6 years to be 6.4 μ g/dL, which was higher than that in the present study. Such a higher value could be a result of the lead in the drinking water from roof catchment systems, where Vog-related acid rain tends to leach lead from nails, solder, or paint and into drinking water.

Measurements of low levels of lead in blood are fraught with many technical problems. Contamination of test tubes and lab equipment may increase the true lead concentration up to 150%³. Capillary samples also might be contaminated with lead from a finger. Considering these factors, the actual blood lead levels in Hawaii could be even lower than this study indicates. The lab that used only venous samples and a particular type of vacutainer designed for heavy metal analysis had the lowest blood lead mean (3.4 μ g/dL). It is unfortunate that not all participating clinics agreed to draw venous samples into blue-top vacutainers.

Information from the questionnaire provided very little explanation about the variation in lead levels among study participants.

FIGURE 4. MEAN BLOOD LEVELS BY AGE, LABORATORY, AND TYPE OF PHLEBOTOMY

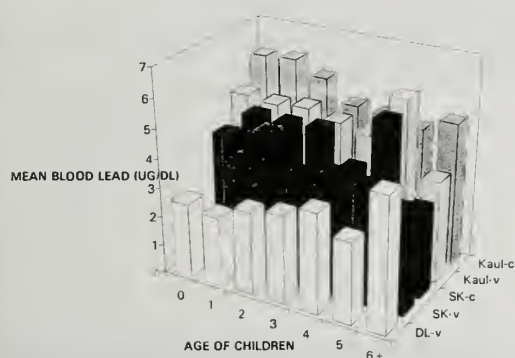


TABLE 4: Blood Lead Means (μ g/dL) for Selected Risk Factors

		NO		YES	
		Number	Mean	Number	Mean
BEHAVIORAL RISK FACTORS	Chew on toys	192	4.3	144	4.7
	Eat dirt	271	4.4	64	4.7
	Pick paint	231	4.4	97	4.7
	Eat paint	309	4.5	18	4.9
	Fingers in mouth	80	4.1	259	4.6
	Chew on furnitures	281	4.4	57	4.8
	Use pottery, cans or ceramics for food	175	4.5	161	4.5
RESIDENTIAL RISK FACTORS	Urban neighborhood	181	4.4	139	4.7
	Separate house	122	4.7	150	4.2
	Home older than 30 yrs.	225	4.3	105	5.0
	Peeling paint in home	194	4.4	131	4.7
	Recent paint removal	230	4.5	76	6.4
OCCUPATIONAL RISK FACTORS	Battery work	301	4.4	29	5.1
	Metal work	302	4.4	28	5.1
	Demolition	315	4.5	13	3.8
	Radiator repair	303	4.4	26	5.4
	Plumbing	310	4.5	18	4.1
	Sandblasting	317	4.4	12	5.4
	Auto body work	294	4.4	35	5.1
	Painting	273	4.4	56	4.7
	Welding	295	4.3	34	5.7
	Other lead handling	308	4.7	17	5.0
HOBBIES INVOLVING LEAD		225	4.4	2	4.5
SOCIO-ECONOMIC FACTORS	Mother is homemaker	169	4.2	162	4.8
	Mother's education more than high school	168	4.5	156	4.6
	Father's education more than high school	154	4.5	98	4.6
	Income less than \$15,000	218	4.4	96	4.8

Numbers in bold/italics indicate that the mean among the exposed is statistically significantly greater than the mean among the unexposed ($p < 0.05$).

Considering the large number of factors analyzed, several variables are expected to be statistically significant just by chance. Even with respect to the few statistically significant variables, the actual difference between mean levels was less than 1 μ g/dL. The largest difference in lead levels seemed to be related to the laboratory where the analysis was performed.

Our study was unable to identify any new risk factors for high blood lead levels.

Other possible explanations for the low blood lead levels found in this study are: Low soil and air levels due to steady circulation of fresh air, relatively small percentage of homes built before 1950, good maintenance of old houses (many of them are located in neighborhoods with high property prices), high percentage of time spent outdoors and the comparatively good nutrition status of children in Hawaii. The low levels in Maui may be a result of selection bias: All children on Maui were recruited through private physicians and only venous blood samples were taken. Another explanation could be the higher proportion of newer housing on Maui; 32% of all housing on Maui was built since 1980, as opposed to 21% overall in the state. Only 19% of housing on Maui was built before 1950 as compared to 27% in the state (Census Data 1990).

Conclusions

1. The mean blood lead level of 389 children was found to be 4.5 μ g/dL and none had levels above 14 μ g/dL. If more children had been tested, a few children with levels above 14 μ g/dL might have been identified.

2. The level of parental knowledge and concern about lead and by health professionals varies widely. Overall it appears to be rather low. In combination with a widespread reluctance to subject a child to a phlebotomy, it resulted in a low participation rate in blood lead testing.

3. Children living in different geographic areas and housing types, with varying socioeconomic and educational backgrounds, were included in our study. Thus, despite the high refusal rate, there is no reason to think that the true distribution of blood lead levels among children in Hawaii differs drastically from our results.

4. Based on our study, mandatory lead testing of all children in Hawaii is not recommended. However, health care providers should routinely inquire about risk factors, such as flaking paint in old houses, parents' occupational exposure to lead, rainwater catchment systems, toys and hobbies that might be contaminated by lead. Children exposed to any one risk factor should be tested. However, living in a house older than 30 years cannot be regarded as a risk factor unless flaking or chipping paint is present.

5. Public education dealing with sources and risks of lead is essential in preventing exposure to lead in the future and in achieving an appropriate level of diagnostic suspicion.

ACKNOWLEDGMENTS

Federal funding was provided by the State Legalization Impact Assistance Grants, Family Support Administration, Department of Health and Human Services. All of the expenditures for research assistants, laboratory costs and printing for a total of \$17,000 were covered by these funds. Thanks are due to the staff of Kapiolani Medical Center, Kaiser Permanente, Waianae Coast Comprehensive Health Center, Kokua Kalihi Valley Clinic, Waimanalo Children's project, PACT in Kalihi, Hawaii Children's Centers, and Olivet Baptist Preschool. Appreciation also is expressed to the members of the "ad hoc" group, who planned much of this work.

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(Continued on page 250) ►

MAKA O KE KAUKA

RUSSELL T STODD

The future is not what it used to be!

In what was planned as a love fest, the President's lady, Hillary Rodham C., appeared before the American Medical Association House of Delegates on June 13th and expounded on her perceptions of what is the best approach for health care for the American people. She did her best to charm those in attendance by paralleling the AMA's agenda from cleaning up CLIA and hassle factors to tort reform, and all points in between. Her poise, delivery, demeanor and oratorical skill were those of a highly trained performer (read, trial attorney), but substance was lacking. No particulars of legislation, funding, controls, mechanisms, nor any reality was forthcoming. Still, the revelation was that of a planner who knows that her efforts will be fruitless without the cooperation of organized medicine.

Nothing can be done in one trip.

The new administrator at HCFA is Bruce C Vladeck, formerly president of United Hospital Fund of New York and a member of the Prospective Payment Assessment Commission, which advises Congress on hospital payment issues. He stated that any additional modifications to the Medicare program should be "modest", and that the hefty cuts suggested by some members of Congress would not come about. (right away)

There ought to be one day—just one—when there is open season on senators. (W Rogers)

The Clinton budget promises "cuts", except that neither side is admitting that spending will increase next fiscal year, and the year after that, and etc. "There is more dishonesty in this town than I've ever seen," says Sen. Brock, (R. Tenn.). This brings to mind the campaign promise to reduce White House and Congressional staffs by 25%, but of course, that did not happen. Believe this—it is becoming increasingly evident that the thing that is eating away at American democracy is the set of privileges that allows Congressional types to leverage incumbency into lifetime sinecure. Latest polls show that 70% of Americans favor term limits for Congress.

Let us give until it hurts. You go first.

"We all must sacrifice," and who better to begin with than those "fat-cat, profiteering doctors." So, Medicare reimbursement is trimmed again, with cataract surgery leading the cuts, now

down 36% since 1986. No doubt, as our cataract-mill, advertising brethren continue to promote eye surgery as only slightly more debilitating than a haircut, the reimbursement will continue the downward spiral. Having found a golden goose, they seem determined to pump Medicare until the cataract goose is reduced to feathers.

It's not the frivolity of women that makes them so intolerable. It's their ghastly enthusiasm. (H Rumpole)

Bill Clinton appointed Joycelyn Elders, MD to replace Antonia Novello, MD as Surgeon General. He appointed 3 females sequentially to be Attorney General before he finally got one who could accept the job, Janet Reno. He named DeeDee Myers to be White House spokesperson, appointed Donna Shalala to be director of HHS, and Madeleine Albright to be ambassador to the UN. He appointed another woman, Ruth Bader Ginsberg, to be Supreme Court Justice, and he also named a woman, Lani Guinier, as assistant Attorney General for civil rights, but she was dispatched before undergoing scrutiny by the Senate. For some reason not yet explained, he appointed a male, Warren Christopher, for his secretary of state. I do not wish to impugn the character or qualities of any of these appointments, but one might ask if President Clinton (Billary?) missed the target in his selection of Mr. Christopher.

Politics is the skilled use of blunt objects.

In Arizona the optometrists have been trying for years to get their therapeutic bill through the legislature, but each time accurate medical testimony prevailed to defeat the measure. This year, the Speaker of the Arizona House wanted the bill passed, so in a sly abuse of power, he bypassed the health committee, placed the bill in the commerce committee, quietly tacked the measure onto a minor piece of

legislation, and got the bill signed by the governor before a motion for reconsideration could be presented. And the moral is—even eternal vigilance can be circumvented by a devious special interest.

There is no passion like that of a functionary for his function.

Bureaucratic overkill department—As Dave Berry would say, I am not making this up. A Man in Linden, New Jersey, lost his lunch after taking a radioactive iodine pill for a thyroid condition. Poised to protect the public, the NJ Department of Environmental Protection declared the lost meal radioactive waste. They dispatched an inspector and waste-disposal crew, complete with masks and gloves, to clean it up. Furthermore, they ordered the city to send a police car, fire truck and emergency vehicle to assist in the operation. What, no SWAT team?

It was beautiful and simple as all truly great gifts are.

Eye surgeons one and all owe a large round of applause and a grateful thanks to the Guild of Prescription Opticians of America who have contributed over \$60,000 to the Tissue Banks International for research into the causes and cures of eye disease. The local chapter of Guild Opticians has been an active participant and has always demonstrated an abiding willingness to work with the Hawaii Ophthalmological Society. Aloha nui loa.

Addenda

- ▲Of 31 AIDS patients treated with ganciclovir for CMV retinitis, 81% responded and 61% achieved a complete response that resulted in a non-progressive, inactive scar.
- ▲Life can only be understood backward, but it must be lived forward.

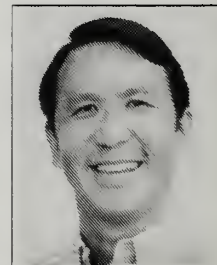
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A singer. A board-certified family practitioner. Soft-spoken for a New Yorker. Ron Richmond knows. . .

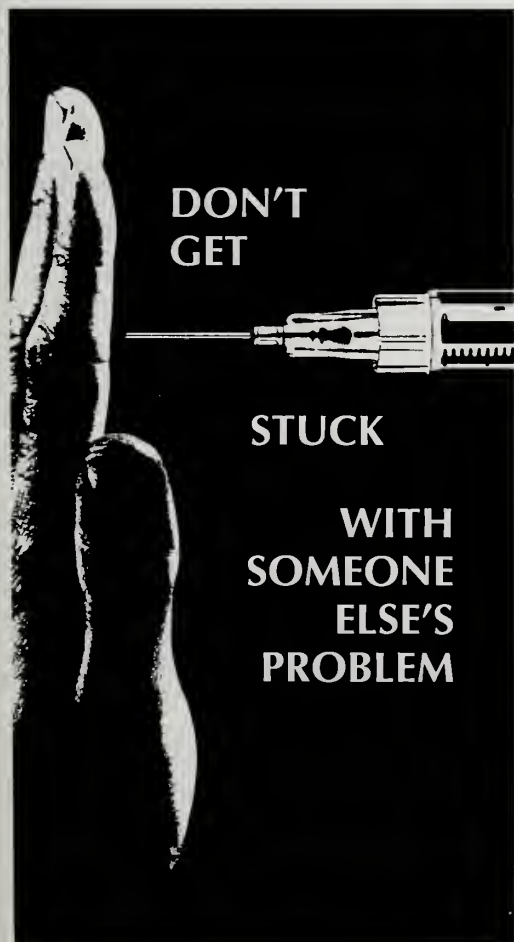
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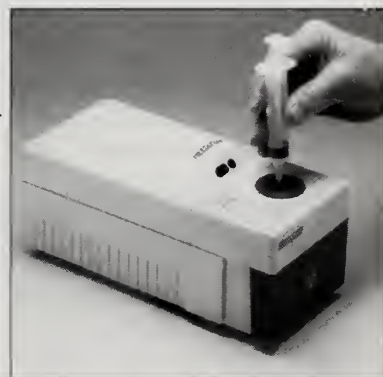
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Ma'i Ulu

In this issue of the *Journal*, we recognize our neighbors to the south—Amerika Samoa.

American Samoans have the rights of citizenship in the USA. Our community includes a great many Samoans and Samoan athletes have put Hawaii on the world map. The coming and going between here and Samoa fill the air-planes.

It seems quite appropriate, therefore, that we have a research article on a public health issue in Amerika Samoa—"Stroke and Traumatic Brain Injury in that southern Pacific group of the islands—known to Samoans as *Ma'i Ulu*."

The author, Gloriajean L Wallace PhD, researched extensively on the subject while she was based in Hawaii at the University during the last decade. She is a speech-language pathologist with imposing credentials and has had a particular interest in the health and well-being of the Samoan people.

J I Frederick Reppun MD

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WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t $_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C $_{max}$ of warfarin but did not produce any changes in its anticoagulant activity (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC $_{0-12h}$ for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C $_{max}$, and T $_{max}$ for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a \geq 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also taking other drugs (e.g., ketoconazole, spiroclonolone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear (Wallerian) live degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/– mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 150 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg/day and in rabbits at doses of up to 50 mg/kg/day. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following events have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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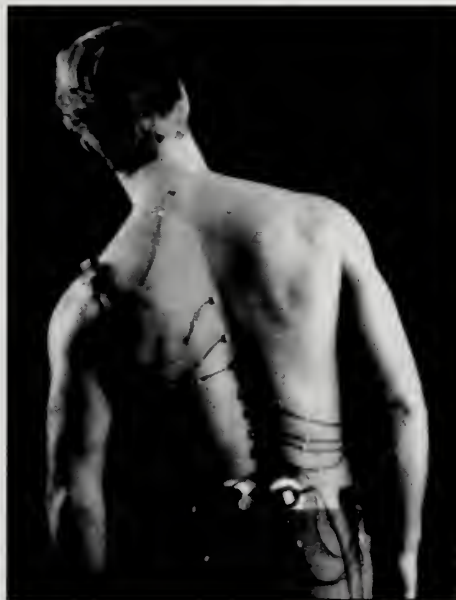
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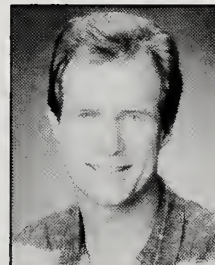
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Barry Morrison
Loan Officer

Highlights of the HMA Council Meeting of August 6, 1993

Members present were: J Chang, A Don, F Holschuh, J Spangler, C Kam, R Stodd, L Howard, C Lehman, B Shitamoto, M Cheng, R Goodale, HKW Chinn, P Chinn, HH Chun, W Dang, Jr, P Hellreich, S Hundahl, R Kimura, M Shirasu, C Wong, P Kim, J Betwee, H Percy, T Smith, J Lumeng, N Winn, J Kim, J McDonnell; F Reppun, Editor, HMJ; Legal Counsel Vernon Woo; Auxiliary representative, S Wong, Medical Student Rep, A Matteo; HMA Staff: J Won, B Kendro, L Tong, J Asato, J Estioko, P Kawamoto and A Rogness, recording secretary.

The treasurer reported that HMA finances are still of concern as membership dropped for the 5th year. Dues now are being considered for some formerly dues-exempt members.

AMA Board Chair Dr. Lonnie Bristow sent a letter congratulating HMA President Jeanette Chang on a successful health care reform meeting with First Lady Hillary Rodham Clinton in Honolulu. He commended Dr. Chang for speaking well on behalf of physicians.

The HMA Auxiliary joined a nationwide movement to change its name officially to HMA Alliance.

Council voted to provide up to \$5,000 toward purchasing whistles for women as promoted by the

American College of Emergency Physicians project, "Blow the Whistle on Violence".

Executive Director Jon Won was asked to attend the initial meeting of the Center for Alternative Dispute Resolution based on a request from State Reps. Joseph Souki and Julie Duldalao to address the issue of prescriptive authority for nurse practitioners.

The Council directed the officers to meet with HMA and the Healthcare Association of Hawaii to discuss the importance of physician input on the issues of collection and use of health care data.

The Council received the announcement by Crossroads Press that it will no longer publish the *Hawaii Medical Journal* as of January 1, 1994; HMA staff and officers are looking at 3 or 4 options regarding the continued publication of the *Journal* and will report back to Council at the next meeting.

HMA's Task Force on Tobacco will testify at the City Council hearing in favor of overriding the Honolulu Mayor's veto of the bill banning smoking in public areas of private buildings.

Fred Holschuh, MD
HMA Secretary



Our old friend, iodine

In this issue we have a case report of a serious illness possibly induced by iodine. The author, Bob Jim, is a senior physician who often has submitted articles on hematology, his specialty, that have been published in the *Journal*.

Considering the wide use of iodine preparations in the practice of medicine, it is somewhat remarkable that there is very little in recent literature that the author researched to substantiate his contention that the thrombocytopenic purpura

probably had a veterinarian preparation as a causative agent.

It would be an interesting follow-up for Bob to have the putative agent analyzed; it would add to the value of the presentation. We also wonder if he reported this case to the FDA. That federal agency might well do a more intensive study since the matter has implications of concern involving animal husbandry and human health.

J I Frederick Reppun MD

It takes a long time to learn

Fortunately, it is happening less often. However, as the combination of two articles in this issue of the *Journal* exemplify, it can happen. We speak of the unthinking, panic-driven attempt at CPR in the face of explicitly documented orders or instructions *not* to do so.


Pediatrician John Briley describes what happened to a little boy with a fatal congenital affliction; his courageous mother helps us all by writing of the anguish the child's parents suffered when such professional instructions were ignored.

The burden of blame need not be saddled onto persons or institutions as yet: It's the system that needs repetitive,

painstaking education and more education.

The reader will have his or her heart wrenched by the two contiguous accounts: "The Tears of Hippocrates" and "Go Gently." The doctor-patient relationship that is the cornerstone of our profession and that our society is struggling to crack apart is cemented back in place by the common anguish of the physician and his patient.

J I Frederick Reppun MD



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Arsenic Toxicity in Hawaii: A Case Report and Review

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The presence of seemingly unexplained peripheral neuropathy in a sick patient warrants persistent delving into the medical, social and especially occupational history. Bearing this in mind, we have an interesting case to present.

Case Presentation

The patient was a 36-year-old man who had been diagnosed as having peptic ulcer disease and the presence of *helicobacter pylori* in an EGD biopsy specimen 3 months earlier. He was admitted to the hospital because of an acute onset of epigastric pain that began that morning. The patient was admitted to the regular medical ward and the gastroenterologist who had been following the patient for his PUD was consulted. The gastroenterologist recommended medical therapy empirically for the ulcers. He believed the patient required a stat EGD since a follow-up EGD done 2 weeks earlier had been negative for ulcers. An H2 blocker medication for *helicobacter pylori* was started. He required 75 mgs of meperidine i.m. for his severe abdominal pain.

The abdominal pain persisted; further work-up included an upper GI series, which showed no ulcers but did show some evidence of duodenitis, and a CT scan of the abdomen that was negative. Laboratory work-up included stool cultures, pancreatic enzymes, sickle cell screen, hepatitis screen, porphyria screen, liver function tests, and ESR, all of which were negative.

The patient described his abdominal pain as being intermittent, excruciating, either localized in the epigastric region, the left lower quadrant, or sometimes everywhere; it was associated with nausea but no vomiting. On physical examination, there was no rebound or guarding but mild to moderate tenderness to palpation could be demonstrated. He continued to complain of abdominal pain throughout his hospital course, and he required a constant regimen of pain control including Demerol, Dilaudid, Darvocet, Percocet, and even a PCA pump with low-dose morphine.

The patient's abdominal pain work-up was completed without any significant findings. He was discharged to outpatient care with pain medication, an H2 blocker, and medica-

tion for *helicobacter* prophylaxis. He was instructed to return for follow-up in a clinic in a couple of days.

When he reported to the clinic, he still complained of severe abdominal pain and had taken all of the pain medicine given at discharge. During this visit, a 24-hour urine heavy-metal screen was obtained. The report came back negative for lead and mercury but was positive for arsenic at 865 mcg/liter (normal < 100). To confirm this urine arsenic finding, pubic hair analysis for arsenic was done and it also returned positive at 5.6 microgram/gram of hair (* 75% have less than 0.03 to 0.3 mcg/gm hair, 20% are between 0.3 to 3mcg/gm hair, 5 % are up to 4 mcg/gm hair.) A more detailed diet and work history was obtained. He was treated as an outpatient for arsenic toxicity with penicillamine. However, he presented himself again to the clinic with the same, severe abdominal pain before penicillamine therapy. He was again admitted to the hospital for treatment with dimercaprol or BAL (British Anti-Lewisite), which entails intramuscular injections every 4 hours. The patient improved clinically, the repeat 24-hour urine-arsenic level was < 35 mcg/liter, and the arsenic content in the hair was down to 1.3 mcg/gram of hair.

The patient continued to be followed closely as an outpatient. His abdominal pain reoccurred with a fluctuating course. Additional work-up revealed a negative colonoscopy, a negative nerve conduction test and electromyelogram and negative lab tests, including urine and hair arsenic levels. Many questions were raised: Was this definitely arsenic toxicity? If so, what was the source of the arsenic? Were the GI symptoms related to the arsenic toxicity?

The Sources of Arsenic

Arsenic is ubiquitous in nature and the 20th most common element in the earth's crust¹. Arsenic is present in saltwater and seafood. Fish and shellfish contain a relatively high concentration of arsenic; this is relatively nontoxic and is readily excreted through urine². Urinary arsenic levels may be increased as much as tenfold after eating a large seafood meal¹. Notably, arsenic also is found in well water³.

Historically arsenic has been used in medicines⁴ and currently organic arsenicals are still being used in the treatment of certain protozoan diseases. It is also an ingredient in veterinary medicine⁵. Arsenic has been used in feed for poultry, cattle and swine to improve the nutritional status of animals⁶. Furthermore, arsenic has been a constituent of drugs such as opium⁵. Industrial use of arsenic has been a major source of worker exposure. In 1973, the National Institute for Occupational Safety and Health estimated that 1.5 million

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people were potentially exposed to arsenic during the course of their work⁷. Smelter workers were at increased risk for potential arsenic exposure. A study of smelter workers indicated increased mortality—mostly secondary to lung cancer—proportional to their exposure to arsenic⁸.

Arsenic is used in many commercial products; it is used as an additive in metal alloys to increase hardening and heat resistance, in the manufacture of glass, in wood preservatives, in lead-plating, and in various types of paints including fresco, tempera, watercolor, and oil paints⁹.

Arsenic also is used in making silicon microfilm⁴, light-emitting diodes in watches⁹, and in salt-impregnated materials for fires to produce multicolored flames¹⁰. Arsenic also plays a major role in agriculture: Pesticides, herbicides, fungicides, weed/tree killers, fly killers, rodenticides all contain arsenic because of its effectiveness and low cost¹¹. The use of arsenic as a desiccant of cotton comprises 15% of the U.S. market for arsenic trioxide. Significantly in our case, arsenic trioxide is a commonly used agent in the treatment of wood against termites. The wood used in the construction industry in Hawaii often is pressure-treated with this compound.

Clinical Manifestations of Toxicity

The clinical manifestations of arsenic toxicity vary widely and are dependent on the duration of exposure, level of the dose (if ingested), whether intake is acute or chronic, and on the chemical compound of the arsenic. The 3 forms of toxic arsenic are the trivalent salt, pentavalent salts, and arsine gas¹². Elemental arsenic is not toxic¹². Pentavalent salts are found in the earth's crust and are prevalent in foods; they are less toxic than the trivalent salts which tend to accumulate in the body more readily. Arsine gas is the most toxic and is frequently fatal.

Acute toxicity can occur with arsine gas poisoning or with massive doses of ingested arsenic. The symptoms of acute arsenic intoxication are apparent within 30 to 60 minutes, but death usually does not occur until approximately 24 hours later¹³. A garlicky odor in the breath and stool may be apparent. The patient might complain of a metallic taste in the mouth¹⁴.

Arsine gas poisoning is usually overwhelming and usually leads to death. Initial symptoms include: Fever, headache, nausea, vomiting, epigastric pain, dysuria, and explosive diarrhea. Hemolytic anemia also occurs as the arsenic binds to red blood cells; cyanosis and hypoxia could ensue. Shock with intractable vascular collapse and encephalopathy can occur, and myocardial damage and bone marrow suppression.

Acute ingestion of arsenic is usually more insidious in its manifestations. Severe gastrointestinal involvement is the hallmark of acute ingestion. Symptoms can include nausea, vomiting, profuse watery diarrhea and colicky abdominal pain¹⁴. Dysphagia secondary to the toxic damage to the esophageal lining can occur, as well as dehydration and electrolyte abnormalities. Other gastrointestinal manifestations include jaundice, hepatomegaly, hepatic enzyme abnormalities and even pancreatitis.

Almost every organ system can be involved. Cardiorespiratory findings include EKG abnormalities such as QT prolongation, nonspecific ventricular arrhythmias and sagging of the ST segment^{15,16,17}. Pulmonary edema, bronchial pneumonia and pericarditis can occur. Neurological manifestations include seizures, encephalopathy, headache, vertigo, and a sensorimotor neuropathy which occurs 10 days to 3 weeks after the exposure¹³. Hematologically, anemia is the

most common (normochromic-normocytic, hemolytic). Other findings include leukopenia, aplastic anemia, leukemia, and thrombocytopenia¹⁴. Renal failure and proteinuria secondary to cortical necrosis can occur and a case of severe rhabdomyolysis with the CPK elevated to 31,350 U/L in a fatal arsenic trioxide poisoning has been reported¹³.

Chronic arsenic exposure is associated with several other abnormalities in addition to some of the features of acute arsenic poisoning. One of the most characteristic abnormalities of chronic toxicity involves the skin. Dermatologic manifestations include: Hyperpigmentation (arsenic melanosis), brawny desquamation, hyperkeratosis (especially of the palms and soles), alopecia, dermatitis, folliculitis and "rain drop" depigmentation^{12,14}. Skin cancers have been known to appear in 5% to 10% of people with chronic exposure to arsenic. The cancers can appear 5 to 25 years later and appear mostly on the trunk and upper extremities. Histologically, the lesion can be either squamous cell or basal cell¹².

The content of arsenic in nails and hair has been used for diagnosis of chronic exposure. Aldrich-Mees lines (white transverse bands across fingernails and toenails) can be seen 4 to 6 weeks after exposure^{14,19}. An elevated concentration of arsenic in the hair is a sign of chronic toxicity. The upper limit of normal content in individuals not exposed to arsenic is said to be approximately 5mg/kg but the arsenic content in hair can vary depending on environmental and nutritional factors²⁰.

Other manifestations of chronic toxicity include squamous cell carcinoma of the lung and liver abnormalities such as hepatocellular carcinoma, post necrotic cirrhosis and heman-gioendothelioma. In Taiwan, peripheral vascular (Blackfoot) disease has been associated with high exposure to arsenic in well water¹².

Other Reported Cases in Hawaii

In the search for other cases of arsenic toxicity in Hawaii, we contacted the pathology departments of most of the major hospitals in Oahu, as well as Smith Kline Laboratory, Diagnostic Laboratory Services of Hawaii and the Hawaii Department of Health. There were several cases reported to the Department of Health, but all of the reports were dismissed as high urinary arsenic levels secondary to seafood ingestion rather than to arsenic toxicity. One patient at Kaiser Permanente Medical Center presented with peripheral neuropathy. Work-up revealed elevated urinary arsenic levels 1300 mcg/l and 372 mcg/l (normal < 100 mcgA) and an elevated hair arsenic level of 151 mcg/100 gram of hair (normal 0-65 mcg/100gram). The source of his arsenic exposure was unknown.

As a result of our investigation, there were no other reports of arsenic toxicity in Hawaii that were documented by positive urine and hair analysis.

Diagnosis and Treatment

A carefully detailed history regarding the possible source of the exposure is extremely important when considering arsenic toxicity as a diagnosis. In addition to the history and physical, laboratory tests are useful—some more than others. Serum arsenic level is often not helpful because of rapid clearance. A 24-hour urine collection is useful, especially for documenting acute arsenic intoxication. Arsenic is excreted through the kidney at a rate of 30% to 70% in a 24-hour period²¹. Toxic levels might be missed if there is a delay between

(Continued) ➤

the time of exposure and the time of evaluation. In acute ingestion, abdominal radiographs might be useful because arsenic, a heavy metal, will show up radiographically²².

In chronic exposure, analysis of nails and/or hair is helpful though the arsenic content of hair is affected by nutritional and environmental factors. Arsenic is present in hair and nails 2 to 4 weeks after ingestion³. One paper reported analysis of arsenic in other biological fluids, such as gastric and vesicular fluids that accumulate higher levels as compared to pleural and pericardial fluids²³. There is no standardized value or a definitive test that diagnoses the arsenic toxicity absolutely, although urine arsenic levels greater than 200 mcg/l and hair arsenic levels greater than 65mcg/100 grams of hair can be used as a presumptive evidence of an increased arsenic load²¹.

Treatment should be directed in 2 ways: Chelation therapy to increase excretion of arsenic and supportive and symptomatic therapy for the organ systems involved in the toxicity. The Poisindex²⁴ at the Hawaii Poison Center recommends the following treatment: "For acute massive arsenic ingestion, cardiac and respiratory support using compressors and ventilators, as in any other critical patient is recommended. This should be followed by gastric decontamination with gastric lavage and an absorbent such as activated charcoal, or a cathartic magnesium citrate or a sorbitol solution. Alkalinization of the urine might be helpful in preventing deposition of red blood cell breakdown products in renal tubular cells when hemolysis is occurring."

Chelation therapy is recommended in symptomatic patients known to have ingested arsenic and in asymptomatic patients who have a documented urinary arsenic level greater than 200 mcg/l. Dimercaprol is the first line of treatment. The dose ranges from 3 to 5 mg/kg i.m. every 4 to 12 hours until the symptoms abate or another chelator is substituted. One author recommends tapering the dose but continuing administration of dimercaprol until the urinary excretion is less than 50mcg/24 hours¹. Dimercaprol is an effective chelator but has some disadvantages. The intramuscular injections can be painful, and there are many adverse effects such as mild systemic shock, tachycardia, hypertension, vomiting, convulsions, headache, nausea, vomiting and anorexia. A prior injection with epinephrine might alleviate some of systemic effects²⁵. D-Penicillamine is an oral chelator found to be effective. The usual dose is 25 mg/kg given 4 times a day up to one gram/day. The 3 short-term adverse effects have not been reported, but long-term effects of penicillamine have included fever, leukopenia, thrombocytopenia, eosinophilia and renal toxicity. Another agent, 2,3-dimercaptosuccinic acid (DMSA), appears to be a promising method of treatment, although currently it is approved only for use in lead-poisoning in children. DMSA for adult arsenic treatment is still under investigation and, therefore, must be obtained from the Regional Poisons Unit²⁷.

Summary

As mentioned at the beginning of this article, many questions were raised in our one particular case including the problem of verifying true arsenic toxicity and in determining the source of the exposure. In our case, there was a markedly elevated concentration of arsenic in samples of pubic hair and in the sample of urine.

While arsenic toxicity can present with GI symptoms, we felt that in this particular case the association of the abdominal pain with arsenic toxicity was unlikely. For one, the patient's symptoms persisted despite apparent adequate treatment for arsenic toxicity. Also, the usual symptom of chronic arsenic toxicity is peripheral neuropathy (which was not documented in our case) and not abdominal pain. After the exhaustive diagnostic workup, we felt that this patient had irritable bowel syndrome and that the discovery of arsenic toxicity was serendipitous.

In regards to the etiology of the toxicity, the patient's occupation involved working in the construction industry for a number of years. He indicated a definite exposure to termite-treated wood throughout that period. Wood for building houses, etc. is commonly pressure-treated with an arsenic-based compound; therefore, this source of occupational exposure appears to be a likely one.

Another remotely possible source was the ingestion of contaminated illicit drugs. Cases of the use of illicit drugs laced with various toxic agents such as cyanide and strychnine have been reported. Although our patient required analgesics not commensurate with his symptoms, he categorically denied any use of "street" drugs. The random urine drug screen for such was negative. The patient also claimed he was subjected to a series of random urine drug screens at the job and all had been negative.

In conclusion, our patient represented what appeared to be a well-documented case of arsenic toxicity. However, further investigation was needed as to whether the source might have been prolonged exposure to chemically treated wood. In that eventuality, medical practitioners need to consider arsenic toxicity in their differential diagnosis of patients presenting, in particular, with peripheral neuropathy of unknown etiology, and should obtain an appropriate occupational history.

ACKNOWLEDGEMENTS

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CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: General, Enalapril Maleate: Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis. Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, Drug Interactions, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided. (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Enalapril Maleate and Hydrochlorothiazide).

Pregnancy, Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality, below.)

Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no

10
mg



25
mg

alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats, and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide, Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4, 5, 6 mg/kg/day (approximately 1-2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Neonatal Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: General, Enalapril Maleate: Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dose reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69[®]) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See Drug Interactions.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake may also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmias and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see Drug Interactions, Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the

treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathetomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients: Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: Enalapril Maleate: Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium. **Hydrochlorothiazide:** When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vitro* mouse

bone marrow assay:

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: re-assay, reverse mutation assay with *E. coli* sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenetic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drivaphile* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *A-yeppilins-nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy, Pregnancy Categories: C (first trimester) and D (second and third trimesters). See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Enalapril and enalapril are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Poliatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences, peculiar to this combination drug, have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, Cough.

Clinical Laboratory Test Findings: *Serum Electrolytes:* See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Other adverse reactions that have been reported with the individual components are listed below, and within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, Hemodialysis Patients); *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction; pulmonary edema, rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic [jaundice]), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported, a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, pyelonephritis; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, hearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

Hydrochlorothiazide—Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), saladenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

For more detailed information, consult your DuPont Pharma Representative or see Prescribing Information.

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Thrombocytopenia Associated with Exposure to Iodine

Robert T S Jim MD*

Iodine as a cause of thrombocytopenia is not listed in hematology textbooks. A Medline search over the past 10 years reveals no such occurrence. In this report a patient exposed to iodine developed profound thrombocytopenia.

Case Report

A 24-year-old Samoan-Chinese man who was a dairy worker developed bruises and petechiae. When seen 3 days later, other than the hemorrhagic skin findings, no other physical abnormalities were found. A CBC revealed WBC 12,400/cmm, RBC 4.66 million/cmm, hemoglobin 14.3 grams, MCV 89, MCH 30.6, MCHC 34.6. The differential smear showed segs 88, band 1, lymphs 7, monocytes 4%. The platelet count was markedly depressed at 8000/cmm and the reticulocyte count was 1%. ANA, RA factor, and serum protein electrophoresis were all normal. Total serum iodine was 9.8 ug/dL (normal 4.5-10.0).

Bone marrow examination revealed marked megakaryocytic hyperplasia.

For the previous 2 to 3 months he had been spraying dairy cows' udder teats with Teat Dip, a glycerin-iodine solution containing 0.1% iodine, as a prophylactic against mastitis. The patient was advised to discontinue all further use of Teat Dip spray.

Prednisone 80 mg a day P.O. was started and 10 units of platelets were given for nose bleed on day 7. Two days later, the platelet count had risen to 25,000/cmm, but dropped sharply to 11,000/cmm by day 11. Therefore, danazol 600 mg/day was added on day 12 for a greater immuno-suppressive effect because it was apparent that prednisone in the dose given was not effective. Because of the decreasing platelet count and the severity of the thrombocytopenia, splenic radiation also was started on day 12 at a dose of one Gy. Thereafter, 6 biweekly fractions were given for a total of 6 Gy over a 3-week period. Six and a half weeks after onset of the disease the platelet count again was severely reduced to 3000/cmm and the dose of danazol, therefore, was increased to 800 mg/day. Vincristine 2 mg i.v. and gamma globulin 25 grams i.v. also were given.

Prosorba immunoabsorption resin column therapy initiated a month earlier and 6 daily column treatments were given because of the decreasing platelet count and high risk for clinical bleeding, especially in the brain in a young person.

The platelet count had risen rapidly to 70,000/cmm as a result, but then dropped to 40,000/cmm a week later. It finally rose to 436,000/cmm at 2 months post-onset and remained normal.

The platelet count was 415,000/cmm at 7 months. Prednisone was gradually reduced and had been discontinued at 2 months, the danazol was discontinued at the same time.

Throughout his entire illness, the patient was treated as an

outpatient. The return of his platelet count to normal took 27 days (platelet count of 160,000/cmm).

Other than the exposure to iodine, no other causes for the thrombocytopenia could be elicited. Which modality of the multiple therapies was the most effective could not be determined, and in all probability, all of the combined therapies contributed to his recovery.

Discussion

Although there is no direct proof that iodine spray used to treat the dairy cows' udders had caused thrombocytopenia, in this case a causal relationship is strongly suspected. To expose this patient to the iodine again in order to attempt to re-induce the thrombocytopenia to prove a direct cause and effect was unwise and highly risky.

Isolated thrombocytopenia caused by iodine or iodides has not been reported in the recent past. Preparations of iodine and iodides include Lugol's solution (iodine), sodium and potassium iodide solutions, expectorants containing sodium or potassium iodide, radioactive iodine (sodium iodide L-131); antiseptics, such as Betadine, containing povidone-iodine in the form of ointments, solutions, skin cleansers, surgical scrubs and vaginal suppositories; and x-ray-contrast material also contains iodine. Teat Dip contains free iodine mixed with glycerin.

The adverse effects of iodine and iodides include chronic iodine and iodide intoxication (iodism), usually dose related, such as unpleasant taste (described as brassy), burning in the mouth, sore mouth and throat, hypersalivation, painful sialadenitis, acne, rash, productive cough, diarrhea, coryza, sneezing, upset gastric irritation, weakness, foul breath, fever, depression, and occasionally goiter if large doses are given for long periods. In the treatment of nontoxic nodular goiter, administration of iodine can increase plasma thyroid hormone and cause thyrotoxic symptoms. Adverse effects of the topical and vaginal iodine-containing ointments and solutions include local redness, irritation, swelling, pain and burning.


Individuals occasionally are very sensitive to iodine or to organic preparations containing iodine, especially when given i.v. Acute reactions can occur almost immediately or can occur several hours after administration. Angio-edema of the larynx leading to dyspnea and suffocation can occur; skin hemorrhages, serum sickness manifestations such as fever, arthralgia, lymph-node enlargement, and eosinophilia could occur. Thrombotic thrombocytopenic purpura and fatal periarteritis nodosa have been described².

Individuals who are sensitive to iodine or iodide by any route should be cautioned against its use.

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Tears of Hippocrates/Go Gently

John M Briley Jr MD*

Kim Bode**

I encouraged Kim Bode to allow me to include the piece she wrote for Hospice. It follows immediately after this article. Any of you who have lost a child would understand, once you've read her story, why it should be shared.

Tears of Hippocrates*

As little Khris' pediatrician I considered it a privilege to work with him and his family, but it was equally heart-rending to lose him and watch his parents work slowly through their loss. It hasn't been easy for them. But then, you readers already know that or you wouldn't be reading this publication.

I remember Khristopher Bode as never complaining about all the procedures I had to perform. Of course, he would look at me apprehensively, but never with dislike. And every now and again he would look at me with the merest hint of distrust, but never with distaste. While grateful for this gentle reception and forgiveness, my task was made all the harder.

I remember Kim, his mother, facing her problems alone while her husband frantically begged the Army for a transfer from Boston. I remember trying to be supportive, but as Khris's pediatrician I was more often than not the relayer of bad news. But like her son Khris, Kim never complained. I remember my own sense of frustration. I could do nothing more for little Khris, of course, but guilt can gnaw at a doctor's ego like a demon. Emotion—even unreasoning emotion—given half a chance, will always overcome logic.

Which brings me to the subject of guilt. Specifically, parental guilt.

As Oliver Goldsmith observed: "What art can wash guilt away?" Indeed, once guilt has been inflicted it cannot be taken away. Picture taking a feather pillow to a high mountain on a windy day. Imagine ripping the pillow open and scattering the feathers to the wind. Now, gather every single feather in the valley below and far beyond, and then stuff it with all its fellows back into the pillow. The ability to accomplish such a feat would be roughly equivalent to what it would require to remove a guilt which has been set in motion.

Unfortunately, Khris' parents had guilt laid on them, and, I am sorry to say, by my brethren in the medical profession. Hippocrates said, "At least do no harm." We doctors—and nurses—would do well to heed that sage piece of advice. If Hippocrates were alive today, he would shed tears.

What happened? Though we had decided to keep Khris comfortable in every sense, we had also decided, after much discussion, to allow Khris a peaceful and dignified death. If he fell asleep peacefully and didn't breathe, we would not resuscitate him. We agreed that our only caveat was that if he

was struggling for air we would suction him and give oxygen; if he was hungry we would feed him; and if he was thirsty we would give him fluids. And at all times, of course, he would be cuddled and loved. And he was. A lot.

Well, Khris did start to die peacefully in his sleep, but the nurse on duty pushed the "code blue" button. The emergency room crew crashed into the room and resuscitated Khris. Unfortunately, I was at the office at the time and couldn't stop them, and they didn't heed the pleas of Khris's parents. Khris, though weaker than ever, was now thoroughly frightened. And the parents were thoroughly upset. I was phoned and, along with the parents, told the emergency room crew to back off. I also delivered the message to the floor nurse.

Then, unbelievably, the head emergency room doctor told the parents: "You realize, of course, that your child will die?"

Although this was in no way true, the terrible words had been hurled, the underlying cruel and unfair accusation had been leveled, and the road to guilt had been paved. This is why Kim says, and says with great restraint: "Certain comments were made that only increased our feelings of guilt and horror." I marvel she can put it so mildly—but then, she is a lady.

To top it off, after Khris did die (peacefully) the nurses would not allow the mother to stay with her dead infant, even for a short while. She charitably refers to this as having "met with resistance from some of the hospital personnel," because she believes the nurses truly meant well. But for a long while after Khris's death Kim felt she had never had the chance to say goodbye to her son. More guilt due to our insensitivity. Fortunately, we now know that parents should have time with a dead child; just as we know that, like an adult, a child deserves a comfortable and dignified death. Any ridiculous and emotionally counterproductive medical-legal aspects to the contrary notwithstanding.

I can only hope all of us in the medical profession have also learned to "let go"—to remember that though we are expected to save lives, that how we handle death is as least as important as how we handle life.

Go Gently**

As though it were only yesterday, I can vividly recall the events surrounding the birth of our son Khristopher. After many long and hard hours, he was delivered safely it seemed.

I remember the absolute joy in knowing I had a son, but he was whisked away rather quickly because of the complications of birth. All I knew while lying in the recovery room was that I had to go down the hallway and count fingers and toes. The nurses would not allow me up—or so they instructed me. Hugging my i.v. pole for support, I took the long walk to see my son. Nothing was going to stop me.

Khristopher, a handsome, smiley little baby with deep blue eyes, had the temperament of an angel. So for months I

(Continued on page 282) ►

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** The bereaved mother

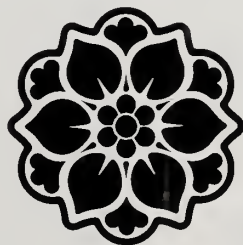
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Chester J Adessa Jr⁺

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National health-care costs are continuing to climb and employers in Hawaii and across the nation are forced to increase their share of the burden. To limit these costs, worksite health promotion programs are increasing in number and in scope. Smoking control programs in particular now rank as the most prevalent type of worksite program; as the disability, absenteeism, and early death on the part of smokers have been well-documented as contributing to the cost of health care. Our research describes a year-long, pilot smoking-cessation program implemented at Hawaiian Telephone Company. Our program used a combination of behavioral-modification, social support and incentives technique to assist people to stop smoking or to maintain their nonsmoking behavior. The 12 volunteer participants provided a multiethnic, long-term, heavy smoker employee sample. Survey results at 1 year demonstrated that 4 of them quit smoking (quit rate=50%), 2 reduced their tobacco intake, 2 dropped out of the program and continued to smoke. The 4 who had entered the program for maintenance purposes remained smoke-free. Cost-benefit analysis yielded conservative estimates indicating that the program had paid for itself and saved an additional \$350 a year per participant who remained a nonsmoker.

Introduction

Reducing the rising cost of health care has been a national priority. Despite this increasing concern, health care expenditures have risen at nearly twice the rate of the gross national product¹. One response to higher health care costs has been to shift payment from the public to the private sector. Business, in particular, has become a major payer of health care costs since most health insurance is organized and financed through the workplace⁷. In 1987, business contributed \$135 billion in health care spending, of which \$97 billion was spent on health insurance. In addition, business spent another \$11 billion on workers' compensation

and temporary disability insurance medical benefits¹. As a result of these large expenditures, more than 81% of employers responding to a national survey indicated a major concern was health-care cost management³.

In Hawaii, the financing of health care by business is well established. Because of the enactment of the Prepaid Health Care Act in 1974, most employers have been required to offer health insurance to their employees working at least 20 hours a week. Presently, plans are underway to expand the employer's role in financing health insurance in Hawaii by mandating coverage of employee's dependents as well⁴.

As payment for health care continues to shift toward business, employers in Hawaii and across the nation are placing new emphasis on a number of health-care cost management strategies to contain expenditures. These strategies include company self-insurance, health insurance plan refinement, disability guidelines management, and health program development such as injury prevention, employee assistance and health promotion.

The most common type of worksite health promotion activity is to control smoking⁵. Nationally, 35.6% of businesses reported having smoking control programs³. The prevalence of smoking control programs is probably due to research that has demonstrated it costs more to employ smokers than nonsmokers. Although there is no single agreed-upon estimate of the cost of employing smokers, one estimate of annual cost to the employer per smoker is between \$336 and \$600⁶.

The negative health and behavioral cost of smoking has been clearly documented in terms of increased risk for chronic obstructive lung disease and cancer⁷. Studies have shown that smokers use health-care facilities 50% more than nonsmokers and tend to die or retire sooner than nonsmokers⁸. According to a Surgeon General's report, smokers are also estimated to be absent from work 33% to 45% more than nonsmokers. These increased rates of absenteeism are estimated to represent a loss of 81 million working days in the United States⁹.

In Hawaii, the cost reflects national figures. It was estimated that smokers in Hawaii cost \$173.6 million in direct medical expenses and lost productivity during 1985. This cost amounted to \$174 dollars per Hawaii state resident¹⁰.

According to the 1989 Behavioral Risk Factor Surveillance Survey of Hawaii residents, 23.9% of employed respondents were smokers. The survey also demonstrated that smoking was associated with other health risk behaviors such

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as alcoholism (i.e. binge drinking, chronic drinking, and drinking and driving), seatbelt non-use, and sedentary lifestyle¹¹. Together, the number, cost, and associated health risk behavior of employed smokers provides a clear rationale for worksite smoking control intervention.

Control at the Worksite

Smoking control programs at the worksite vary in scope and intensity ranging from smoking prohibition, incentive schemes, treatment approaches and a combination of strategies⁷. The most common intervention, namely a restriction or prohibition of smoking at the worksite, could also be one of the simplest and most economical methods¹². According to the National Survey of Worksite Health Promotion Activities, 76.5% of worksites have a formal policy on smoking³. However, research has demonstrated that smokers who are not allowed to smoke at work tend to smoke more when outside of the workplace³. For example, Gottlieb and associates found that a restrictive worksite smoking policy can be effective in reducing environmental exposure to tobacco smoke at work but not at decreasing smoking prevalence¹⁴. Thus, smoking policies, such as a ban on worksite smoking, might not be effective in reducing the ill effects of smoking on employee health unless combined with other approaches.

Programs based on incentives include quit-smoking contests and reward systems for maintaining a smoke-free status. Nearly a quarter of the employers across the nation are estimated to have offered special events or contests³. In one incentive program, smokers were given lottery tickets for each week they maintained abstinence. Lottery prizes included weekly and quarterly winnings¹⁵. Other programs offered non-monetary rewards, such as praise and recognition. Regardless of the type, incentives appear most successful when they are offered in moderate amounts yet frequent intervals for good behavior which the individual can control. Incentive programs have also demonstrated effectiveness when they are consistent with organizational policies and tailored to target group characteristics¹⁶.

The approaches to treatment range from behavioral strategies, such as self-help to medically based programs which offer advice by physicians and nicotine substitutes. Behavioral programs that include both individual and group approaches are being implemented with increasing frequency¹⁷.

Nationally, 54.3% of employers offer information regarding smoking effects on health, 49.7% provide self-help materials, 20% utilize group classes or workshops and 15.1% offer individual counseling³. Quit rates at worksite-smoking-cessation programs seem to produce results comparable to clinic-based pro-

grams. For example, workplace smoking programs can be expected to offer sustained quit rates of 20% to 30%^{18,19}. Programs that provide a combination of strategies have achieved the greatest success. This is especially true of programs that offer motivational strategies with training skills^{12,20}. One employer who conducted a multicomponent smoking control program reported that 20% of the smoking workforce quit smoking¹².

Savings in Costs

Depending on the type and success of smoking cessation programs, conservative estimates indicate that employers can save \$175 to \$345 annually per smoker. These savings are associated with the reduced costs of employing a healthier, more productive work force⁶. The exact savings to employers the result of a smoking cessation program depend on the cost

(Continued) ►

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of the program in relation to participation and quit rates²¹. Aside from savings for the employer, direct gains to the smoker are achieved in reduced disability, illness, and premature death¹².

In general, monetary concern has not been shown to be the primary factor in instituting a smoking control policy. According to the National Survey of Worksite Health Promotion Activities, companies developed smoking policies for the following reasons: To protect nonsmokers (40.4%), to comply with regulations (39.5%), to protect equipment (12.7%), and to protect employees who were at high risk for health problems (7.4%)³.

Local Experience

The Hawaiian Telephone Company (HTC) is one example of an organization active in health promotion. As a self-insured organization, HTC maintains extensive data on employee health. In 1984, benefits paid due to absenteeism (ie, missed hours of work due to illness or injury) totaled over \$2 million. Health-care expenditures consumed 13.9% of HTC's net income in 1980 and 17.7% in 1990. Aware of their climbing health-care costs, HTC made a commitment to employee health through corporate and site-specific programs and policies.

Approximately 23% of HTC employees are smokers. HTC piloted a year-long smoking-cessation program in an effort to convince employees to stop smoking, and in that way to reduce health-care costs. In anticipation of adopting a total smoke-free workplace policy, the pilot program also gave

HTC an opportunity to test smoking-employee reaction to such a proffered policy change.

The pilot program began in May 1990 as a joint effort between the American Cancer Society (ACS), HTC Customer Services, and HTC Health Services Department/Fitness Center. The Cancer Research Center of Hawaii (CRCH) conducted the evaluation of the pilot study.

Our research describes the program which used a combination of behavioral-modification, social support and incentives techniques. The target population was a multiethnic, long-term, heavy-smoker employee population.

Methods

Employees eligible to participate were smokers in the Customer Services Department of approximately a total of 500 employees. Smokers were personally invited to participate in the pilot program by the manager of customer services.

The sample included 12 volunteers. Their average age was 38 years. Eleven of the participants were women. The ethnicity of the respondents was varied and included Caucasian, Japanese, part Hawaiians, part Filipinos, and others. The majority of the participants had some college education and a stable employment history at HTC. The average educational level was 1 year of college. The number of years participants had been employed at HTC ranged from 1 to 27 years with an average length of employment of 14 years. Participants included salaried managers and hourly paid staff.

The history of smoking by participants indicated they were mostly long-term, heavy smokers. For example, 75%

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of the participants indicated they had spent 20 or more years as a smoker. The average number of cigarettes smoked per day was 30.

Intervention

The program emphasized life-style changes the key factor in achieving smoke-free status. It included 3 components: Attending a stop-smoking clinic, skill-development classes and a social support group. The program was held after work in the company main building and sessions lasted from 1 to 2 hours. Membership fees in the company's fitness center were waived in order to encourage the participants to exercise during the program.

The stop-smoking clinic component closely resembled the traditional approaches to the problem. In the clinic sessions, participants were instructed on ways to quit. These sessions were offered twice weekly for the first 2 weeks of the program by an ACS facilitator.

Skill-development classes included sessions on weight control, nutritional management, exercise, hair/make-up, fashion styling, stress reduction and money management. These classes were intended to build participants' self-esteem by improving their appearance and personal confidence. Classes were offered twice a month throughout the program year and topics were rotated. All of the instructors were volunteers from the community.

The support group was organized under the guidance of an ACS facilitator. The support group meetings provided a forum for participants to share their feelings and discuss problems. It met once or twice monthly throughout the program.

In order to motivate individuals to participate actively in the program, a point system and a package of incentives were offered. For example, participants received points for maintaining ideal weight, achieving weight loss, exercising, and for attending skill-development classes and support group sessions. In addition, they also received points for time spent as a nonsmoker. The participant with the greatest number of points at the end of the program was awarded the grand prize of a trip to a Neighbor Island. Second and third place winners also received gifts. All participants who completed the program were awarded a certificate.

Analysis

Survey questionnaires were issued 1 year after the program start, in order to obtain information on the background of the participants and to evaluate the program. All 12 participants responded to the survey; however, not all questions were answered.

Records were also kept on the cost of the program so as to conduct a cost-benefit analysis. Self-reported smoking status was confirmed by direct observation by the participants co-workers and supervisors.

Results

Of the 12 participants who started the program, 8 entered the program as smokers attempting to quit and 4 entered as nonsmokers seeking maintenance. At the end of the program year, 4 had quit smoking, 2 had reduced their tobacco intake and 2 had dropped out of the program and continued to smoke. Of the 4 who entered the program for maintenance, all maintained a smoke-free status. The quit rate or the number of smokers who were able to quit smoking was 50%, although actually 8 of the 12 became or continued to be nonsmokers.

(Continued) ►

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Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral alpha-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

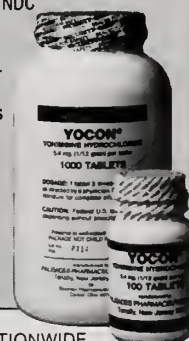
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

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For those who were able to quit or maintain a smoke-free status, participation in the program for a full year appeared to be an important factor in their success. Of the nonsmokers at the end of the program, six (75%) participated in the program for the full year. One individual of the 4 who continued to smoke completed the program and 2 quit without participating for the entire program year.

The results indicate that participants had been reluctant to quit smoking in the past. For a few participants, this was their first effort at quitting; whereas the majority of participants had tried previously to quit at least once, but no more than 4 times. The number of attempts at quitting seemed very small when the number of years participants had been smoking is considered. Past methods of quitting included cold-turkey approaches, and involvement in other organized smoking cessation programs.

Half of the respondents agreed they felt healthier since they had stopped smoking; 42% agreed that they felt more productive at home and at work. Comments about the benefits of being a nonsmoker included "clear breathing," "not as tired," "fewer colds," and "more confidence."

Comments on the point system yielded seemingly contradictory findings. Although most participants found the point-tracking system hard to follow and over 60% did not know their own score, over half of the group thought the point system helped to motivate participation in program activities. Suggestions for improving the point system included awarding an equal number of points to each participant at the start of the program, more precise guidelines, and having a scorekeeper to update and post scores.

The most helpful aspects of the program ranked in order of importance included: 1) Specific techniques on how to quit, 2) group support in suggesting ways to not start smoking again, and 3) more information about managing stress. If given the repeat opportunity to change their own involvement in the program, several people indicated they would monitor their diet more carefully and attend exercise classes. If given the opportunity to change the program itself, respondents suggested that more specific information should be provided, and group discussions facilitated on reasons for quitting and concerns related to expected withdrawal symptoms. Other suggestions included scheduling fewer meetings as group goals are met, and avoiding classes in December around the Christmas holiday.

Discussion

The results of the pilot study appear to indicate that a combination of behavior modification, social support, and providing incentives makes for an effective program for individuals attempting to stop smoking, as well as individuals seeking to maintain their nonsmoking status. The \$1,400 cost of the pilot program paid for incentives, fitness memberships, awards, and food at the mid-year and year-end banquets. Most of the work involved in administering the program was volunteered by the ACS and CRCH, or by HTC employees.

HTC estimates that smokers cost between \$200 and \$1,500 a year more than nonsmokers in medical expense, short-term disability and decreased productivity. The estimate for increased health-care costs alone is over \$350 a year per smoker. The savings to the company, therefore, could be estimated conservatively at \$350 per smoker a year. Four employees who no longer smoke at a savings of \$350 each or

\$1400 total, result in the program paying for itself. There will, of course, be additional savings for every year each of the employees continues to be a nonsmoker while employed by HTC. Four other employees participated in the program as part of their maintenance program. If any of those participants go back to smoking, the company would lose the \$350 savings. Therefore, in addition to those who actually quit, the savings arising from at least one of the participants who maintained nonsmoking can be included in the cost savings of the program. Five employees also reported increased productivity at work and home, which is difficult to quantify, but should be considered as a further value of the program.

In summary, the most conservative assessment is that the program paid for itself and improved the health status and quality of life for half of the participants. A more likely assessment is that the program saved at least \$350 in year one and will save \$350 a year for each employee continuing to be smoke-free while working for HTC. In fact, the program saved \$1,400 in year one, will save \$350 a year for each employee continuing to be smoke-free, and additional benefits will be experienced through improved productivity and better employee moral.

The significance of this intervention is enhanced by the reason of the participants having been long-term, heavy smokers. The difference in life expectancy of a 38-year-old nonsmoking woman compared to a heavy smoker is almost 16 years²². The difference between a light smoker (<24 cigarettes a day) and a 38-year-old heavy smoker is almost 13 years²². The combined years of life extension due to the program for the 4 participants who quit is 64 years.

Evaluation of the program was a critical component of the design, implementation and success of this pilot project; previously, only 17% of worksites with anti-smoking activities reported they had conducted formal evaluations³. In our project, the program evaluation information was presented to the participants, the facilitators and HTC management. Data from the evaluation will serve as the basis for future health promotion policy in order to provide programs in a systematic fashion tailored to the specific needs of the population at hand.

ACKNOWLEDGMENTS

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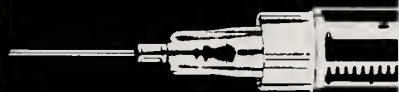
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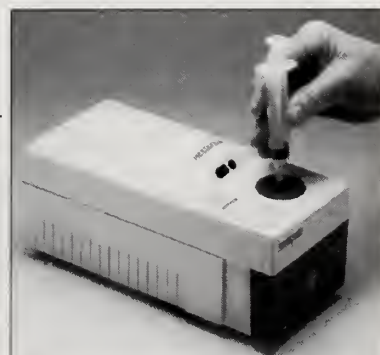
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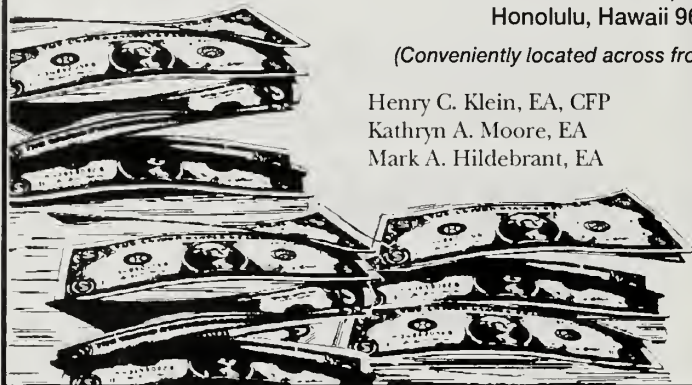
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Toxic strains of the finely filamentous, velvety, dark-olive green to black algal organism, Microcoleus Lyngbyaceus, (formerly Lyngbya majuscula Gomont, or "lyngbya") have been recognized as etiologic agent of "stinging seaweed" dermatitis (one of several forms of "swimmer's itch") in Hawaii since the late 1950s as reviewed¹. Lymphadenopathy, pustular folliculitis, and local infections have been reported in some persons^{1,2}.

Introduction

In 1959 it was reported that a gram-negative pigment-producing bacillus was the predominant bacterium isolated from marine *Lyngbya majuscula*^{1,2}. In 1961 it was reported that a nonhemolytic streptococcus was cultured from the aspirated contents of a scrotal vesicle in a stinging seaweed dermatitis patient². That same report mentioned that neither *Candida albicans* nor dermatophytes were identified. We describe the results of culture and sensitivity determinations for specimens of *Microcoleus lyngbyaceus* algae collected during a toxic algal outbreak.

Materials and Methods

Specimens of organisms tentatively thought to be *Microcoleus lyngbyaceus*⁴ tentatively were obtained during an outbreak of "stinging seaweed" dermatitis at Kailua Beach, Oahu, Hawaii, on September 8, 1979 and were examined by light microscopy as fresh- and formalin-fixed material.

A representative of the Hawaii Department of Health Pollution Investigation and Enforcement Branch obtained surface seawater specimens in sterile containers approximately 50 yards off-shore on February 15, 1984, from areas on Maui labeled the Lahainaluna area and the Lahaina Broiler area. Undiluted (0.1 ml) and diluted (1:100) samples of seawater were plated directly onto marine agar. A specimen of *Microcoleus lyngbyaceus* obtained on February 4, 1984 from the south side of Lahaina near the Puamana subdivision was streaked directly onto marine agar.

The marine agar plates (kept at 26° to 27°C) were examined at 24- hours, 48-hours, and 1-week of incubation for signs of growth. Representative bacterial colonies on the marine agar

plates were sampled and gram-stained. Bacterial colonies of gram-negative rods were then inoculated onto triple sugar-iron agar with 50% seawater while colonies comprised of gram-positive rods were inoculated onto tryptose broth made with 50% seawater. Seawater (0.01 ml) and seaweed specimens also were cultured on Sabouraud dextrose agar and incubated at 25° to 27°C for 2 weeks in order to isolate streptomycetes. Culture isolates then were characterized using physical/biochemical identification tests and antibiotic sensitivity tests.

Since initial screening of seawater and *Microcoleus lyngbyaceus* algal specimens revealed indole-positive vibrios and *Vibrio alginolyticus*, more samples from areas endemic for stinging seaweed dermatitis and/or stinging seaweed were obtained. *M. lyngbyaceus* algal specimens and seawater specimens were obtained from the same area of south Lahaina, Maui (ie, south of Lahaina Shores near the Puamana subdivision) on September 1, 1984, and from the Anini Beach area near Hanalei Bay on the island of Kauai on September 3, 1984. The Lahaina shorebreak seawater salinity was 14 parts per thousand (ppt) and the Kauai shorebreak seawater specimen salinity was 13 ppt; whereas Hana, Maui, freshwater stream control sample measured 0.2 ppt, as measured by conductivity methods.

The specimens for culture were serially diluted with phosphate-buffered saline and plated onto marine agar and TCBS (thiosulfate-citrate-bile salts-sucrose), a medium selective for vibrio bacteria. All cultures were incubated at 37°C. The plates were examined for bacterial growth at 24 and 48 hours. Representative bacterial colonies on the plates were sampled, gram-stained, and characterized using the API 20E identification system. Indole-positive vibrios were selected and further characterized as isolates of indole-positive (IND+) and tryptophan-deaminase negative (TDA negative) suggesting the presence of indoles and not free tryptophans (eg, *lyngbya*-toxin-A and/or *lyngbyatoxin*-A precursors).

On September 7, 1985, a specimen of seawater and algae consistent with *M. lyngbyaceus* was collected from surface water at the Kahala Beach ocean shoreline on Oahu from which *Vibrio alginolyticus* was recovered.

Results

The bacterium *Vibrio alginolyticus* was cultured from marine specimens of the blue-green algal organism *Microcoleus Lyngbyaceus* obtained from 3 endemic areas of toxic stinging seaweed, namely Anini Beach on Kauai, Lahaina, Maui and Kahala Beach, Oahu. *Vibrio alginolyticus* was cultured from *M. lyngbyaceus* in seawater as well as from moist *M. lyngbyaceus* recovered from the beach (ie, as beach wash) at Lahaina, Maui. The *Vibrio alginolyticus* recovered was a gram-negative rod that formed yellow mucoid colonies on TCBS agar. The *V. alginolyticus* was sensitive to conservative antibiotic activity of

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+++ Microbiologist

chloramphenicol, gentamicin, tetracycline, sulfadiazine, and trimethoprim/sulfamethazole.

Discussion

In 1959 it was reported that a "gram-negative pigment producing bacillus" was isolated from *Lyngbya majuscula* Gomont¹. Herein is described the identification of *Vibrio alginolyticus*, a gram-negative rod, from specimens of toxic *Microcoleus lyngbyaceus*. It also has been shown that brackish water can have *Vibrio parahaemolyticus* on and/or in the *M. lyngbyaceus* algae. Both *V. alginolyticus* and *V. parahaemolyticus* histochemically and histologically stain positive for indoles-gram-positive, gram-negative cocci and rods being seen on the algae using Brown and Brenn stains on formalin-fixed paraffin block *M. lyngbyaceus* algae. It is noteworthy that the February 15, 1984 Lahainaluna seawater grew *Moraxella* sp, a group c M-6 *Moraxella*-like bacterium, and *Pseudomonas diminuta*; February 15, 1984 Lahaina Broiler area seawater grew gr. M-6 *Moraxella*-like bacteria, *Providencia* sp, *Vibrio* sp, and *Pseudomonas diminuta*; February 4, 1984 Lahaina Puamana *M. lyngbyaceus* grew *Vibrio alginolyticus*; whereas September 1, 1984 Lahaina, Maui Puamana seawater and *M. lyngbyaceus* grew *Vibrio alginolyticus* and *Vibrio* sp.

Although in one report² it was mentioned that neither *Candida albicans* nor dermatophytes were encountered in a stinging seaweed patient, one species of fungus was cultured from the Kahaluu edge of Kaneohe Bay, Oahu; it came from algal *M. lyngbyaceus*, possibly nontoxic and/or slightly toxic. The fungus was seen as yeast forms within an algal filament, and on culture was black with yeast forms and septated, jointed hyphae. The fungal hyphae were heavily indole-positive to indole histochemistry and indole histological straining. The tips of the Kaneohe Bay *M. lyngbyaceus* algae were faintly indole-positive, suggesting the possible presence of lyngbyatoxin A, aplysiatoxin and debromoaplysiatoxin are 3 tumor-producing substances described in toxin of *Microcoleus lyngbyaceus*—co-carcinogens, or phase II tumor/cancer promoters.

Vibrio parahaemolyticus, and more so *Vibrio vulnificus* can produce blisters, which occurred in a number of patients with *lynbya* stinging seaweed dermatitis. Arsenic occurs in *lynbya* also.

Testing for antimicrobial/antibiotic sensitivity indicated that *Vibrio alginolyticus* is not uniformly sensitive to all antibiotics; however, there appeared to be conservative sensitivity of *V. alginolyticus* to antibiotics listed under results.

ACKNOWLEDGEMENTS

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HENRY N YOKOYAMA MD

Potpourri

Women executives were polled with the question: "Given a choice, would you prefer to live with a man or a cat?" Ninety-five percent preferred a cat. The reasons and rebuttals given were as follows: "Men don't talk much" (but cat's don't talk at all). "Men think the world revolves around them" (well, cats demand a lot of attention, too). "Cats don't miss the litter box" (no comment). (As told by humorist psychiatrist/K Y Lum MD)

The psychiatrist is someone who doesn't have to worry as long as other people do.

Seated on a park bench in New York, an obviously newly immigrated man was saying to an attentive companion: "Emma coma first, I coma next, two assa coma together; I coma again, two assa coma together again. I coma a more, pee pee twice, then I coma for the lasta time." A young lady who was listening was scandalized. She noticed a policeman seated next to them and whispered, "Aren't you going to arrest that terrible old man?" The policeman stared at her, bewildered. "For spelling Mississippii?" (From Playboy Party Jokes)

A couple of small town dogs wandered into the big city. As they roamed the streets, they came across a parking meter. "Look at that," one said to the other, "a pay toilet."

Sportsmen

A friendly voice hailed us as we boarded the UAL flight home from San Francisco. We recognized our favorite physician sportswoman, Shay Bintliff. Nick Price had just won the U.S. Open and golf was on our mind. We recalled that Shay had once been a junior golf champ in Texas. "I was 15 when I won the championship. I asked Patty Berg at a luncheon if I should turn pro; Patty said, 'Shay, you go on to med school—professional golf is rough.'" Shay was also a Class-A tennis player till a soccer accident ruined her knee, and she took up rowing. The crowded plane with the flight attendants looking unhappy reminded Shay of a Herb Caen story. A flight attendant was on his last flight before retirement. An irritating woman passenger complained about her baked potato; he grabbed the potato, slapped it several times, repeating, "You bad potato, you bad potato." He then returned the mashed potato to her tray. She complained no more.

John shanked his tee shot into the woods. Bob, his partner muttered, "That's a lost ball." "No way," bragged John. "That's a special ball. It makes a beeping sound. If you still can't find it, it sends up puffs of smoke. If it lands in water, it bubbles. If it is too deep to reach, it floats to the surface—so it's impossible to lose." "That's amazing," Bob said. "Where can I get one?" "I

really don't know." "Well, where did you get yours?" "I found it." (As related by golfer/humorist, Bill Dang)

"It's All In the Lie."

Hyatt Hotels and Resorts polled 410 executives and nearly half agreed that "the way a person plays golf is very similar to how he or she conducts business affairs." Fifty-five percent admitted cheating at golf at least once. The offenses included moving the ball (41%); not counting a missed tap-in (19%); taking an extra tee shot (13%); intentionally miscounting strokes (8%); and secretly producing a fresh ball while pretending to look for a wayward ball in the woods (6%). (Gleaned from *Time*, Jul 26 issue)

Professional Moves

May: Ophthalmologist Robert Lee Jr opened a branch office at Pearlridge Shopping Center Phase II. Ophthalmologist Anthony Martyak, retired former chief of ophthalmology at Letterman Medical Center in San Francisco joined Gary Edwards and the Honolulu Eye Clinic at Queens POB. Tony was at Tripler from 1981 to 1988, taught as assistant professor at the UH Medical School and served as secretary of Hawaii Ophthalmological Society.

June: Internist Craig Hamasaki opened his office at Kapiolani Medical Center at Pali Momi Suite 420 and St Francis Medical Plaza-West Suite 311.

July: Neurosurgeon William Obana opened his offices at Kapiolani Medical Center at Pali Momi Suite 350 and Queens POB I, Suite 450.

Miscellany

A man only suspected of robbing a cigarette-vending machine was released on \$500 bail until he tried to post bail with only quarters—(Paul Harvey—KHVH radio).

A bank robber successfully got away with his loot. But then he was traced and arrested through a loan application he had filled out before the robbery with his name and address. (Another Paul Harvey story.)

Mr. Glass was terribly overweight so his doctor put him on a diet. "I want you to eat normally for 2 days, then skip a day," the physician said. "Repeat the procedure for 2 weeks. The next time I see you, you should be down 5 pounds." When Mr. Glass returned, the doctor was delighted with his rapid weight loss. "You look great. Did you do this just by following my instructions?" Glass nodded. "I'll tell you though. I thought I was going to drop dead on the third day." "From hunger, eh?" "No," Glass replied, "From skipping." (From Playboy Party Jokes, Aug 1993).

Conference Notes

Migraine Headaches: QMC Friday morning conference May 14, by VP Lee Kudrow. General: Primary headache disorders are:

1. Migraine headaches
 - a. classic
 - b. common
 - c. ophthalmic
 - d. ophthalmoplegic
 - e. hemiplegic
 - f. basilar-vertebral

2. Cluster headaches
 - a. episodic
 - b. chronic
 - c. CPH
3. Chronic muscle contractions
(chronic tension headache)
4. Post traumatic:
 - Type 1: Chronic tension
 - Type 2: Secondary vascular
 - Type 3: Migraine
 - Type 4: Conversion headaches

Migraine Headaches:

Type	Distribution
Classic (with aura)	10%
Common (without aura)	80%
Ophthalmic	Always
Hemiplegic	5%
Basilar-Vertebral	Rare
Ophthalmoplegic	Rare

Discussion: Basilar-vertebral migraine: young women a/c menses; cerebellar symptoms.

Ophthalmoplegic: 3rd nerve paresis, but not involving 4th and 5th nerves; occurs once a year and lasts 2 months; treated with steroids 40mg/d for 1 week.

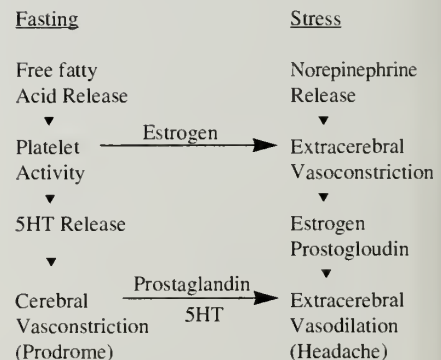
Clinical Nature of Migraine:

Incidence	Female/Male ratio
Children 5%	1:1
Adults 18%	3:1

Common Migraine Profile: Frequency 1 to 3/mos; Duration: 1 to 3 days; Intensity: moderate to severe; location: 60% unilateral; characteristic: 80% throbbing, associated with nausea 50%; vomiting 40%; photophobia: 100%.

Classic Migraine: (scintillating scotomata)

1. Phases:
 - Phase I: prodrome
 - Phase II: Reversible HA
 - Phase III: Intractable HA
2. Provocative Factors:
 - Estrogen changes
 - Dietary Tyramine
 - Post Stress, eg, fasting alcohol
3. Substances (migraine pathogenesis—metabolites of serotonin)
 - a. Hydroxy indole acetate
 - b. 5HT (serotonin)
 - c. Platelets
 - d. Prostaglandins

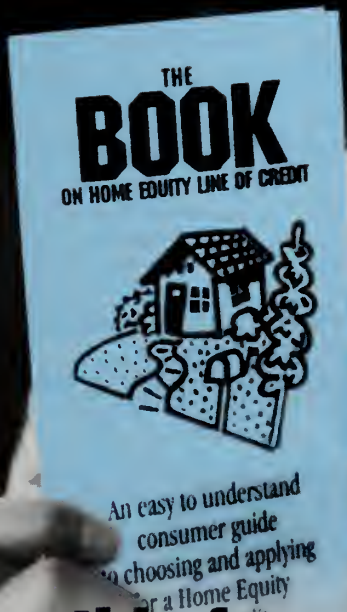


Prophylactic Treatment of Migraine: 2 or more times a month; disabling attacks.

Common Migraine Prophylaxis: twice a month: Inderal 80 to 120 mg/d or Nadol 40 to 80 mg/d.

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With Menses only: Naprosyn 275 mg tid during menses.

Weekend or children: Periacin 2 to 4 mg hs Fri and Sat: 1/2 mg hs (children).

Periacin: Calcium channel blocker; serotonin agonist.

Common Migraine Treatment:

1. No vomiting; moderate pain:
Dramamine tab; wait 30 minutes, give Midrin (2 tabs) and repeat 1 hr later.
2. Vomiting and severe pain. Use antiemetic suppository; wait 30 min, give 2 mg ergotamine; wait 1 hr and repeat prn.

SUMATRIPTIN:

affects only 5HT₁ Others

5HT₂ and 5HT₃ not affected.

Tablets

Relief in 30 min

60% relief in 1 hr

75% relief in 4 hrs

50% pain free in 4 hr

SQ Injections

Relief in 10 to 15 min

50% relief in 30 min

80% relief in 2 hrs

60% pain free in 2 hrs

Effective in cluster headaches (As good as O₂ inhalation)

Wait 10 days between courses of therapy.

Contraindications for Sumatriptin:

- a. Hypertension
- b. CAD (therefore do EKG)
- c. Previous MI
- d. Use of Ergotamine

Side Effects of Sumatriptin:

- a. Chest pain 12%
- b. Tingling scalp
- c. Facial flush
- d. Tingling finger tips
- e. Chest pressure
- f. Tightness in throat

Discussion:

- Oral tablets will be available in 8 to 12 months
- No after-effects
- Can give anytime during attack, ie, early or late
- Side effects in 10 to 12 minutes; start at top of head and work down, ie,
- Tingling or buzzing in head; light flashes; throat tightness; tingling finger tips; chest pain (mimics coronary) (2° to esophageal receptors).

Miscellany

A Des Moines, Iowa, housewife viewing her home half submerged in flood waters commented: "Well, no sense crying about it. It'll just worsen the flood." (Paul Harvey, KHVH radio)

France has reduced the cost of condoms 80% to 15 cents each as an AIDS prevention scheme. (Heard on KHVH radio)

A young woman surfer had a problem keeping her cigarettes dry while surfing. She noticed another surfer kept her cigarettes in a condom. She went to the drugstore and asked: "How do you sell condoms?" The druggist explained that it came in packets of 3 and in different sizes. "Well, it has to be big enough to fit a Camel." The druggist was dumbfounded. (As told by our favorite lecturer, Dennis Meyer at a hyperlipidemia symposium)

Conference Notes

"Malignant Neoplasms of the Skin" WP Daniel Su, professor of dermatology, Mayo Medical School. Friday am July 30 1993. QMC Kam Auditorium.

"How to make diagnosis and how to treat patients right way." Plain talk by a most remarkable lecturer.

1. Malignant Diseases of Skin: Bowen's Disease; squamous cell Ca; Basal Cell Ca; Malignant Melanoma.

A. Bowen's Disease: squamous cell Ca-in-situ; superficial; circumscribed; smiling faces (on cells).

B. Squamous Cell Ca: deeper in dermis; atypical cells.

C. Basal Cell Ca: four features:

1. raw border
2. translucent
3. central ulcer
4. Telangiectasia (most common skin cancer; non-healing ulcer; microscopic features: basophilic; mucin; palisading pattern.)

D. Malignant Melanoma:

1. Lentigo Malignant Melanoma: (Solar Lentigo) Melanoma-in-situ; features: color variegation; irregular border.
2. Acral Lentiginous Melanoma: more common in orientals and blacks; takes 5 to 10 years to invade dermis.
3. Superficial Spreading Melanoma:

more common in caucasians; takes 3 to 5 years to invade dermis.

4. Nodular Melanoma

ABCD of Melanoma:

A. Asymmetry

B. Border Irregularity

C. Color Variegated

D. Diameter Larger

(greater than 6mm²)

E. Kaposi's Sarcoma:

(dark nodules; purpuric; involves skin and mucosa)

1. Classic: in elderly
-Mediterranean
-Slow course
-death rare

2. African
-rapidly fatal

3. AIDS Associated
-rapidly fatal

F. Angiosarcoma:

atypical endothelial cells

G. Lymphangiosarcoma

H. Mycosis Fungoides:

Cutaneous T-cell lymphoma Ddx:
Tinea Corporis (Parapsoriasis)

1. Patch Stage
2. Plaque Stage
3. Tumor Stage (frank lymphoma)

"How to treat right way"

A. Bowen's Disease: excision; biopsy with electrodesiccation and curettage; cryotherapy; Topical 5 FU.

B. Squamous Cell Ca: Excision, Biopsy and E&C; Cryo, Mohs Surgery (take biopsies from 8 margins each time)

C. Basal Cell Ca: Same as above plus Interferon etc.

D. Malignant Melanoma Surgery:

Tumor Thickness	Margins of Excision
<0.76 mm	1 cm margin
0.76 to 1.5 mm	2 cm margin
>1.5 mm	3 cm margin

Node dissection *only* if node palpable
Above criteria may be revised

Immunotherapy:

- a. Monoclonal antibodies
- b. Patient's lymphocytes
- c. Interleukin II
- d. Melanoma vaccine

E. Angiosarcoma: Wide excision; radiation and chemotherapy.

F. Lymphangiosarcoma: Same as above (18 months survival)

G. Mycosis Fungoides:

- Patch Stage: topical steroids, G regimen; PUVA; Topical Nitrogen mustard.
- Plaque Stage: PUVA; topical Nitrogen mustard; conventional X-ray; radiation.
- Tumor Stage: Radiation etc.

Potpourri

It seems that a dog owner in Tulsa, Oklahoma, enrolled his pet German shepherd in one of Oral Roberts University's lavish psychological institutes.

The dog learned to sit, play dead and walk. But when told to heel, the animal would raise his paw to the owner's forehead and howl plaintively. (As told by humorist Rowlin Lichter MD)

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Oncology Dialogue

The weather outside was grim, but the story unfolding inside was just as grim. A 20-year-old woman had complained of vague abdominal discomfort 3 months earlier. An ultrasound showed a left liver lobe mass. She had no history of hepatitis, alcohol or drug use. She appeared slightly cachectic, but had no jaundice or hepatosplenomegaly. Lab studies showed only a slight elevation of SGOT, an Hgb of 10.9 and alpha-feto protein of 54.1. Moderator Ken Sumida pointed out that gastroenterologist Stan Shimoda in a journal article mentions that an alpha-feto protein level of 2,000 was diagnostic of hepatomas. Radiologist Dave Sakuda reviewed CT scans of the abdomen showing metastatic nodules in the peritoneum and diaphragm and a large 5 cm mass in the left lobe of the liver. Pathologist Larry McCarthy described needle biopsies showing large malignant cells consistent with hepatoma and inflammatory cells consistent with chronic active hepatitis. Ken turned to oncologic surgeon Scott Hundahl: "Any room for surgery?" Scott: "She may be a good patient for laparoscopy. If the porta hepatis has nodules, she is not a surgical candidate." Pathologist Grant Stemmerman added, "This is an unusual mode for hepatoma. Usually there are distal mets rather than local peritoneal mets." Scott offered: "Sometimes hepatomas rupture and cause peritoneal dissemination. The 5-year survival for hepatomas with mets is zero. Some may accept the radiographic description, but I would opt for laparoscopic confirmation." David Sakuda took umbrage: "May I make a point about radiographic findings? If it's a

horse, we call it a horse." Scott nodded acquiescence. Ken turned to chemotherapist Dennis Wachi, "Is there a protocol for hepatomas?" Dorothy Coleman from Cancer Research Center spoke up: "We're setting one up." Dennis: "If there is no protocol as yet, the patient might benefit from Adriamycin since her bilirubin is normal." Fellow oncologist Jonathan Cho was explicit: "Whether she is offered radiation, systemic or regional therapy, the goal will be strictly palliative." Ken acknowledged, "It's a grim prognosis for a 20-year-old."

Stemmie's Swan Song
reported by J I Frederick Reppun

Our best-beloved Grant Stemmermann, long-time pathologist at Kuakini Medical Center, was invited by Bob Wong to address the HMA Senior Physician's Committee chaired by Charlotte Florine on June 3. Stemmie gave a most interesting review of 40 years of researching gastric and esophagal cancers involving a comparison between men of Hawaii: white males, Hawaii Japanese and Japanese Nationals. The surgical specimens number close to a thousand. Gems revealed indicated that whites had a predominance of cancers in the cardia of the stomach, and at the lower end of the esophagus or at the junction with the stomach, whereas in the Japanese it was more common closer to the antrum. Smoking and heavy use of alcoholic beverages had much to do with the incidence in both ethnic groups. Here in Hawaii the incidence was predominant in the Japanese and the Hawaiian populations rather than in

the whites. Considering the results of surgical extirpation overall, the Japanese had a better 5-year survival than the whites. The relatively recent discovery of the association with gastric infection by the organism *H. campylobacter*, otherwise known as *Helicobacter* has stimulated much research, particularly because the presence of the organism begins in early childhood and is a social disease associated with poverty and deprivation (it responds to treatment, however). Its presence results in the diffuse type of gastric cancer.

As Stemmie wound up his dissertation, Walter Quisenberry announced that this was probably Stemmie's "Swan Song" because he is leaving Hawaii to move to Cincinnati, taking his paraffin blocks of tissue with him. The reason being that the city has a superb department of microbiology with a large staff of researchers, well-funded and able to study the oncogenes in gastrointestinal tumors.

Stemmie came to Hawaii in 1950 as a pathologist first on Maui, then at Hilo, before starting his stint at Kuakini. He will be returning to Hawaii periodically because his 2 grown daughters and their families reside here. Stemmie belies his chronological age by delving into new and intense research. We wish him godspeed and many happy returns!

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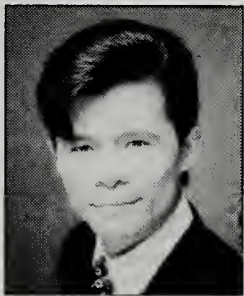
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RUSSELL T STODD

Enough research will tend to support your theory

In a carefully choreographed visit to Hawaii, Hillary Rodham C. hopped around the islands giving evidence to the probable structure of the administration's health care plan. After visiting rural clinics, eg; Hana, Maui, and listening and participating in a spontaneous panel discussing Hawaii's health care system, it appears likely that the linchpin of President Clinton's plan will parallel Hawaii's employer-mandated mechanism. If that occurs, as seems likely, the American Medical Association will be in support, because that is a prime part of the AMA's *Health Access America*. Thus, the AMA, often portrayed as the obdurate, reluctant dragon to all government sponsored plans stands in the forefront of "health care reform."

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Should a cataract surgeon attempt to remove nuclear fragments when the capsule ruptures and lenticular pieces fall into the vitreous? According to Arthur Allen, Jr., MD, director of Ophthalmic Mutual Insurance Company (OMIC), the answer is no. Best action is to continue with the procedure, place an IOL in the anterior segment and refer the patient to a vitreo-retinal surgeon for removal of the lost nuclear material. A recent trial verdict went for the plaintiff, primarily because the jury thought the cataract surgeon lacked appropriate skills to remove the fragments.

We need a President who is fluent in at least one language.

Budget cuts—President Clinton has promised to "root out fraud and overcharges" in the health care system, but the federal office of investigations must endure cutbacks. The result is that Hawaii and 11 other states will slash caseloads to a minimum and open no new cases except under highly unusual circumstances. In 4 other states, the offices are targeted for closure. Congress may pump more funds into HHS investigatory powers, but we are not informed as to cost savings, effectiveness, indictments, or other relative data from past performance.

No amount of political rhetoric can turn a belch into an aria.

As you bemoan Medicare's reduced reimbursement schedule, cast your eyes across the 49th parallel at our physician colleagues in Canada. Under the Canadian single-payer system, fee-for-service physicians are paid on average 41% below Medicare. Procedure-oriented service, such as surgery or endoscopy, are lower still—47% under Medicare. For example, cataract reimbursement is \$440 in Canada (Medicare—\$941), which would hardly meet overhead expenses.

When things are going well, something will go wrong.

A bill proposed by the Indiana Academy of Ophthalmology to restrict laser surgery to licensed physicians was passed by the Legislature and signed into law. The ODs did not oppose the legislation as long as there was no attempt to stop them from removing foreign bodies from the cornea, and there was no physician lobbying to "bash"

optometrists. In Hawaii, no specific statute exists, but the use of lasers is covered in the medical practice standard.

Any attempt to simplify anything only causes more confusion.

Dorothy Sweeney, vice-president of Health Care Group, recommends smaller increases for staff people this year. Six percent to 8% is out for the time being because of reimbursement cutbacks on doctors, and a figure of 3% to 6% is more realistic. Her figures indicate the average annual salary for an employee of 2 to 5 years experience is as follows: practice administrator \$44,100, registered nurse \$29,750, ophthalmic technician \$25,000, billing coordinator \$22,700, computer operator \$19,240, insurance clerk \$19,100, receptionist \$18,200, and file clerk \$14,400. However, retaining excellent people is far more important than shaving a few percentage points from a raise; so, kiss your angels good morning and tell them how much you appreciate their good work—and don't contaminate the soup.

The avoidance of taxes is the only intellectual pursuit that carries any reward.

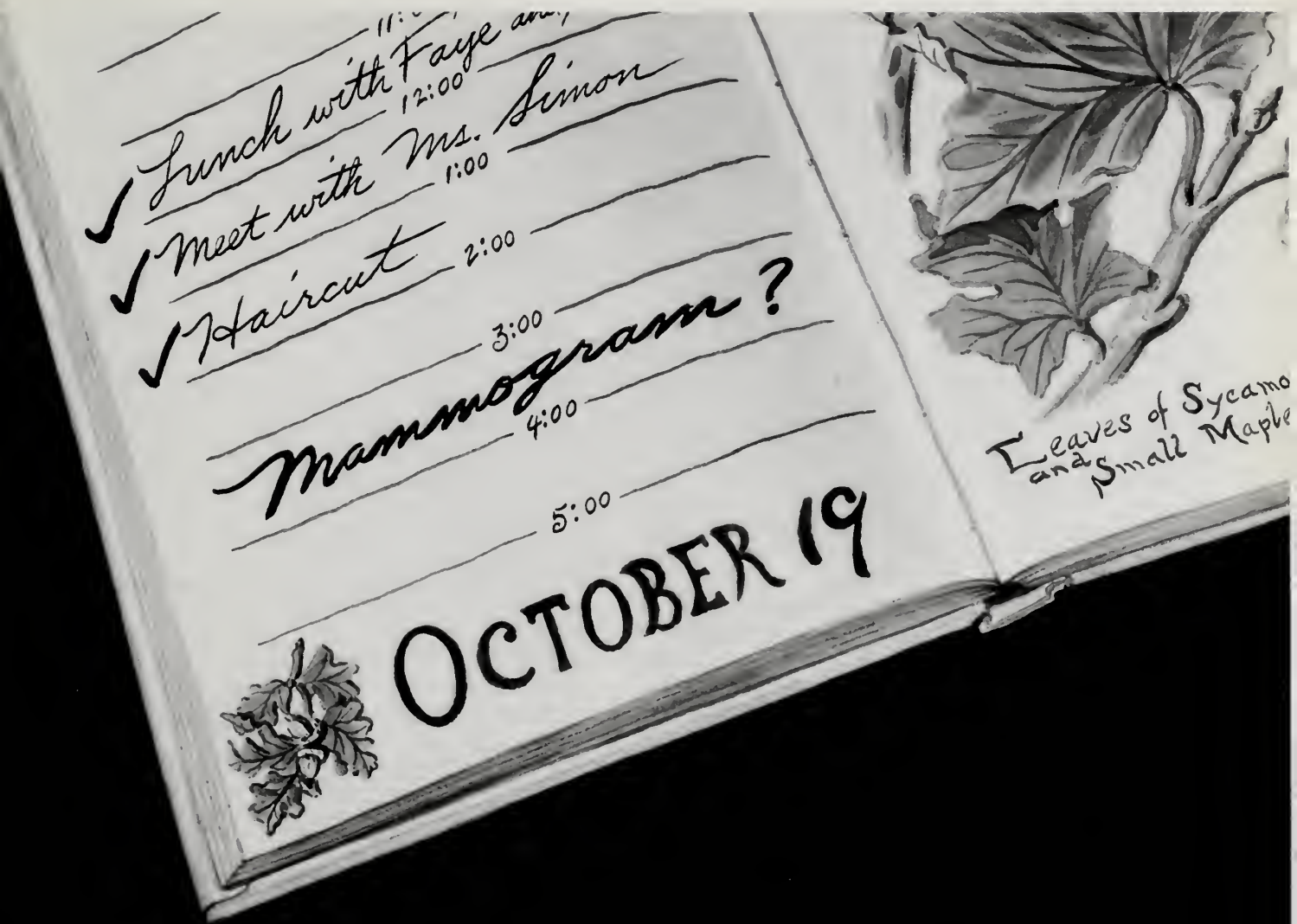
In 1992, Americans donated \$124 billion to charity, easily the most ever and a greater share of their income than in any year since 1963, before the raise of the welfare state. So, it should prove interesting to compare the last year of the "dozen years of greed" with the first year of the "new covenant." With higher taxes, and punishment of "profiteers", one wonders if there will be a disincentive to produce, to save and donate.

Addenda

- ▲ Badminton causes more eye injuries than any other racquet sport.
- ▲ The ingredients in crack cocaine and powdered cocaine are identical, but the criminal-sentencing guidelines treat crack as 100 times worse than powdered cocaine!
- ▲ There is growing evidence that global warming just is not happening, making the President's plan to reduce greenhouse gases to an expensive irrelevance.
- ▲ The goods of fortune still need taste. It is the enjoying, not the possessing, that makes us happy.

Aloha and keep the faith

rts



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thought his inactiveness was due to his gentle temperament. But when he reached 4 months of age I felt something was very wrong. It was.

After many terrible tests, including a muscle biopsy, Khris was diagnosed as having spinal muscular atrophy, a form of muscular dystrophy. The physician was straightforward with us; we would be lucky to have little Khristopher for 6 months. A year would be a miracle. It seemed from that day on his health went downhill.

Khris and I came to Hawaii to escape cold weather. My husband, who had obligations to the Army, was to follow later. So the early period for me was a time of extreme loneliness. Because of all of Khris' problems, complications, and the general stress of his illness, I felt alienated from the world around me. Who could possibly understand my problems or relate to my aloneness? My mother-in-law did the best for me she could: she called Hospice. Until my husband came from Europe, and beyond his coming, they gave me the support I needed.

At the age of 10 months Khris went into the hospital for the second time. He was getting weaker and this time we were told he could no longer eat; we had to learn to tube feed him 4 times a day. It was also becoming more difficult to perform the chest compressions so necessary to prevent mucous accumulation in his windpipe and lungs. But these maneuvers were essential for his life, so we took turns doing them. I believe it was at this point we realized that no matter how hard we fought we couldn't prevent the inevitable. We finally tried to accept reality.

We had thoroughly discussed the use of a respirator, but we decided it was neither for our son nor for us. So upon his third

admission to the hospital, just before his first birthday, we knew our remaining time with Khris was limited.

Khris was resuscitated once, and the procedure was unpleasant for him and the sight was unbearable for us. With the help of our pediatrician, we made the decision to keep Khris comfortable—no respirator, no heroics. We met with resistance from some of the hospital personnel; certain comments were made which only increased our feelings of guilt and horror. But we stayed firm.

Unfortunately, the bitter memory of the confrontation described by Dr Briley will stay with us the rest of our lives. Just 3 days short of his first birthday—Khristopher died. But he died peacefully, with my husband and me and our family by his side. My husband and I believe nothing in the rest of our lives will ever be so hard on us. Yet we would not have managed Khristopher and his illness in any other way.

Khristopher taught us a lot: love, courage, humor, gentleness, and he gave us strength. We were not ready for Khris to leave, but Khris was ready.

On the day of his birth, when I walked down that long hallway to see him, I never realized how long that hallway was going to be.

▲Time has laid his hand

Upon my heart, gently, not smiting it,

But as a harper lays his open palm

Upon his harp to deaden its vibrations.

—Longfellow

Classified Notices

To place a Classified Notice:

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Reference: 1. Jones PH, et al: Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitals, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p < 0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a $\geq 50\%$ rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spiroclonolone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallenian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallenian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p < 0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p < 0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in vitro, with or without rat liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/– mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/m²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthma, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported by other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

THE PRAVACHOL® DIRECTION
IN LIPID MANAGEMENT

Effective lipid management doesn't have to be tough



- Improves key lipids — significant reduction in LDL-C'
- Excellent safety profile
- Easy for patients — once-daily dosing, well tolerated
- Usual dose: 20 mg once daily at bedtime, with or without food


PRAVACHOL®
pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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Highlights of the HMA Council Meeting of September 10, 1993

Members present: A Don, F Holschuh, J Spangler, S Wallach, C Kam, R Stodd, C Lehman, B Shitamoto, R Lee-Ching, M Cheng, R Goodale, H Chinn, P Chinn, W Dang, Jr, R Kimura, M Shirasu, C Kadooka, P Kim, J Betwee, H Percy, T Smith, G Goto, J Lumeng, W Chang, J Kim, A Kunimoto, J McDonnell; W Dang, Sr, B Fong; F Reppun, *Hawaii Medical Journal* editor; Auxiliary representatives J Chuang, S Foo; medical student representative A Matteo; legal counsel Vernon Woo; HMA staff: J Asato, J Estioko, N Jones, P Kawamoto, B Kendro, L Tong and J Won.

John McDonnell, chair of the Membership Recruitment Task Force, announced the senior mentor program for member recruiting is beginning. New physicians in the community will be identified and lists will be provided to leaders in the HMA so they and a colleague from the new physician's specialty society can call on the prospective member to discuss the advantages of joining the HMA and the HCMS.

The Council adopted the recommended budget. The proposed budget was drastically reduced because of the loss of members. The new budget will not contain an increase in membership dues; however, it asks for payment of reduced dues of \$100 by retired and life members. There will be further reduction in staff, and there will be no salary increases; there is little funding for separate programs and serious consideration will be given to cutting down the committee and commission structure. Details will be presented to the House of Delegates for a final decision in October this year.

The HMA Auxiliary reported it will be working with the HMA on the next Distinguished Medical Reporting Awards banquet and roast. HMA will select the recipients of the media awards and the Auxiliary will handle all banquet and fund-raising events.

HMA will submit the names of Jeanette Chang, Danelo Canete, and Santosh Sharma for membership on the AMA Advisory Committee on International Medical Graduates.

Following the announcement that Crossroads Press will not be able to publish the *Hawaii Medical Journal* after December 1993, Council agreed that HMA would publish the *Journal* in-house. The 16-page publication will be printed by Pacific Printers and will be typeset and produced by the HMA communications department. Authors will be asked to submit 2 hard copies of their manuscripts and a 3 1/2-inch diskette to allow transfer to HMJ computers. The advertising will be continued and handled in-house.

Editor of the HMJ, Fred Reppun, announced that because he sensed a new direction from HMA leadership that he believes will limit editorial freedom, he will step down as editor. The Council expressed regret at his decision, and he was given a round of applause for his fine *pro bono* work for the last nine years.

The Hawaii Health Quest Proposal has been reviewed by HMA leadership and a letter will be sent to the State of Hawaii expressing HMA's concerns: 1. Rapid program development without any dialogue or input from physicians; 2. Committee decisions appear to have been made without the knowledge or consent of committee members; 3. A determination without HMA's input, that defines nurse practitioners as primary care providers; 4. Outcome and quality assurance mechanisms appear to be burdensome and excessive; 5. Concern for cost control rather than for benefits and the effect of cost-shifting to the private sector, 6. A co-payment feature that discriminates against physicians and creates a two-tiered system of care.

The Hawaii Foundation for Medical Care presented a report on a meeting with a private firm from Arizona that currently operates both Medicaid and private managed-care programs. It is interested in working with physicians in Hawaii to provide a mechanism to bid on the Hawaii Health Quest Program and, if the Quest program is successful, to branch out to the private sector. Council rejected this proposal.

Fred Holschuh
HMA Secretary

Special Article to the Graduating Class of 1993, John A Burns School of Medicine

Anita L Gerhard MD*

Thank you to the [1993 graduating class of the John A Burns School of Medicine] for the opportunity to address you on this important occasion; it is a great honor and a privilege for me to do so.

This is a very special class for many reasons. You are the first Problem-Based Learning (PBL) class to graduate from this school, and you are graduating at a time when we are all nervously waiting for the announcement of the Clinton health care reforms.

You are also special to me in a more personal way. I first came to Hawaii 4 years ago, and although I have taught students at other schools, we started our career at the University of Hawaii John A Burns School of Medicine at the same time. We have been through a lot together, particularly during our third year. You have given me a lot: Your curiosity, enthusiasm, thoughtful questions—as well as numerous mangoes, grapefruits, oranges, and even fresh fish that you have caught. The close working relationship between teacher and student is one of the most rewarding aspects of being a faculty member here.

So, on this occasion I would like to offer you a gift in return. I wasn't sure what form that gift would take until 2 weeks ago when one of you came into my office bringing strawberries to share. This reminded me of a story that has sustained me in many ways over the years. This story is my graduation present to you. It is from a collection of Zen writings and is called:

A Buddha Parable in a Sutra

A man traveling across a field
encountered a tiger.
He fled, the tiger after him.
Coming to a precipice, he caught hold
of the root of a wild vine and
swung himself down over the edge.
The tiger sniffed at him from above.
Trembling, the man looked down
to where, far below,
another tiger was waiting to eat him.
Only the vine sustained the man.
Two mice, one black and one white,

little by little were gnawing away at the vine.
The man saw a luscious strawberry
within reach.
Grasping the vine with one hand,
he plucked the strawberry with the other.
How sweet it tasted!

Now this story might seem like a rather bizarre gift, so let me explain what it means in the context of a gift to each of you.

What are the tigers above and below you? What do the vine and the strawberry signify?

In terms of your immediate situation, you have just escaped the challenges of medical school [behind you now] and might feel that you are trembling, like the man in the story, at the fearsome prospect of internship and residency ahead [below].

My message to you is this: Don't let the fact that there are challenges to come distract you from the supreme importance of this occasion. Savor this moment, this celebration of your hard-won accomplishment. The maile leis that you have just received from your families and loved ones remind me of the fabled vine, your lifeline. What we have just witnessed, which brought tears to my eyes, is a commemoration of their love and sacrifice, as well as their pride in your achievement. This is an image that I urge you to permanently engrave in your memory. It is the sweet strawberry that will give you faith, hope and sustenance during the long hours that await you in the years to come.

However, the other [far below] tigers that I want to talk to you about today are the challenges that our entire society will be facing. Like the man in our story, we are on a precipice, on the edge of changes in our health care system that will be more profound than anything that has happened since the entire restructuring of our profession during the Flexner era.

Art Buchwald is fond of telling graduating classes: "We are giving you a perfect world—so don't louse it up." I only wish this were true. Problems of escalating health care costs, rapid technological change, fragmentation of care, inadequate access and many other aspects have led to public outcry about the health care system.

Within your professional lifetimes, medicine will change in ways that my teachers could never have imagined. But you have had the good fortune to have a dean and a faculty with a vision of the commensurate changes in medical education. As a result, you have been prepared in a way that no other class before you has ever been prepared for the future.

As faculty, we may not have always given you what you wanted; but I believe we have given you what you will need to succeed and find meaning in this new world. Faculty, like parents, sometimes have to be willing to

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inflict discomfort in the service of our students' growth. There have been many times in the past 4 years when we have insisted that you learn something the hard way, when it might have been much easier for us to have said: "Do it this way, because I said so." Your new curriculum's emphasis on self-directed learning, on teamwork, with the orientation on community, and critical appraisal; these things will be your lifeline, the vine that will sustain you as you face the challenges ahead.

There are some who fear the changes we are about to witness will so radically alter the face of medicine that it will no longer have meaning as a profession. I think this will never occur as long as you also keep your focus on the skills you have learned that are timeless—the art and science of healing. Much of what we currently associate with the practice of medicine is artifact, and is minimally essential to the healing process.

At the risk of using too many metaphors, I would like to tell you another story: One day a woman was about to cook a roast. Before putting it into the pot, she cut off a small slice. When her daughter asked why she did this, she said it was because her mother had always done the same thing when she cooked a roast. The woman's own curiosity aroused, she telephoned her mother to ask her why she always cut off a little slice before cooking her roast. The mother's answer was the same, "Because that's the way my mother did it." Finally, in need of a more helpful answer, the woman asked her grandmother why she always cut off a little slice before cooking a roast. Without hesitating, her grandmother replied, "Because that's the only way it would fit in my pot."

I would like to suggest to you new medical doctors that many of the things that might be lost by changes in our new health care system are not truly essential to our mission as healers. Some things might have been important at one time, but are no longer relevant, like slicing the edge of a roast for a pot that has long since increased in size. Money, entrepreneurial status, independence and power that have been associated in the past with our profession are nice, but they are not the heart and soul of medicine. As you participate in this ensuing process of change I urge you to keep your focus on our patient's best interest, and not on your self-interest.

So—where is the strawberry that I promised you? If you look to your patient's best interest you will find it. Essential to all healing is the physician-patient relationship. As Dr Hilfiker put it: "In this we have an awesome privilege. We are trusted with the darkest secrets, offered the deepest pain and the richest joy, allowed to share in the times of greatest mystery."

The relationship between physician and patient is a sacred trust that must always be honored as such; it is the soul of medicine, and always will be. If you never lose sight of this, then not only will you survive the changes of the future, you will taste the luscious strawberries that this profession has to offer. Medicine is a great profession.

It is a sweet pleasure for me to be able to welcome you as colleagues on this memorable day.

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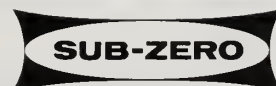
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The Incidence of Meconium-Aspiration in Hawaii

Christian S Sunoo MD*

Thomas S Kosasa MD*

Roy T Nakayama MD*

Ralph W Hale MD*

Meconium in the amniotic fluid was found in 2,633 obstetrical patients and meconium-aspiration occurred in 77 cases out of 14,527 deliveries. Although the incidence of meconium in the amniotic fluid increased significantly at 39 weeks, a corresponding significant increase in meconium-aspiration did not occur until 41 weeks gestation. All deaths associated with meconium, as well as 84% of the cases of severe meconium-aspiration syndrome, occurred in infants born of patients with oligohydramnios and a gestational age of 41 weeks or greater.

Introduction

The incidence of meconium-stained amniotic fluid appears to increase with gestational age^{1,2} but the significance of meconium has been controversial as a risk-factor for adverse perinatal outcome. Meconium does increase the potential for perinatal morbidity and mortality when it is associated with the meconium-aspiration syndrome. The majority of cases of meconium-aspiration syndrome has occurred in association with fetal distress³⁻⁵ but meconium-aspiration has been noted in the presence of a normal fetal heart-rate pattern⁶ and prior to the onset of active labor⁷. The purpose of our study was to document the incidence of meconium present in the amniotic fluid, and to see if a correlation existed with the meconium-aspiration syndrome and advancing gestational age.

Materials and Methods

A detailed review of 14,527 deliveries during the past 2 consecutive years identified 2,633 cases of meconium in the amniotic fluid and 77 cases of meconium-aspiration syndrome. All pregnancy and fetal outcomes were obtained from a careful review of the prenatal, labor and delivery, and neonatal records. Gestational age was determined from a review of menstrual history, ultrasound examination and antenatal records. The gestational ages of all 77 mothers whose infants had meconium-aspiration syndrome were documented by early ultrasound.

Meconium was graded by the physician in attendance as thick, moderate, or thin. The presence of meconium in amniotic fluid obtained preterm was confirmed by spectrophotometric analysis.

In the infant, the diagnosis of meconium-aspiration required finding meconium in the trachea, clinical signs of respiratory distress, and a chest x-ray consistent with meconium-aspiration. Oligohydramnios was diagnosed by ultrasound or by the clinical absence of fluid in the mother documented during labor and delivery.

Meconium-aspiration was considered to be severe when infants had to be placed on a respirator for ventilatory support. All infants with the syndrome were subjected to aggressive airway management. This included pharyngeal functioning with a DeLee catheter at delivery of the head, followed by visualization of the vocal cords and suctioning of the trachea under direct vision by a member of the pediatric house staff. Obstetrical patients who had meconium in the amniotic fluid and whose infants developed the meconium-aspiration syndrome were analyzed in relation to gestational age. Statistical evaluation was done by chi square analysis; the probability was considered to be significant at $P < 0.05$.

Results

The presence of meconium was documented in 2,633 cases (18%) out of 14,527 deliveries between 28 and 45 weeks of gestation. The syndrome itself was diagnosed in 77 deliveries (0.05%). Between 28 and 36 weeks' gestation, meconium was found in 153 cases (10.7%) out of 1,426 deliveries. Between 37 and 41 weeks, meconium was found in 2,305 cases (18.5%) out of 12,487 deliveries. After 41 weeks, meconium was found in 175 cases (28.5%) out of 614 deliveries. The incidence of parturient patients who had meconium in the amniotic fluid, and whose infants went on to have the meconium-aspiration syndrome, remained relatively constant with increasing gestational age from 28 to 36 weeks (Table 1). However, at 39 weeks the incidence increased considerably, followed by a significant increase in the meconium-aspiration syndrome in the infant at 41 weeks (Table 2). A significant increase in the meconium-aspiration syndrome occurred in cases that demonstrated meconium in the amniotic fluid pre-delivery at 41 weeks (Table 3).

The aspiration of meconium by the infant was diagnosed in 7 patients who delivered prior to 38 weeks' gestation. Four of these demonstrated thin meconium and 3 had moderately thick meconium. Very thick meconium was not found in any infant with the aspiration syndrome whose mother delivered prior to the 38-week period. On the other hand, at 39 weeks and beyond, 91% of the infants with the syndrome presented with very thick meconium.


Oligohydramnios was characteristic of 29 out of 31 mothers (94%) whose infants demonstrated the meconium-aspiration syndrome, mothers whose gestational ages were 41 weeks or beyond.

There was a 63% rate of fetal distress and a 57% rate of

(Continued on page 292) ►

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delivery by C-section in the cohort of women whose infants were diagnosed as having the syndrome. However, of the women who had oligohydramnios at 41 weeks or beyond, 90% exhibited fetal distress and 83% of them had to have C-sections.

Term infants with the syndrome spent a mean of 4 days in the neonatal intensive care unit and were hospitalized for an average of 11 days in all. Severe aspiration of meconium was diagnosed in 84% of the infants delivered at 41 weeks' gestation and beyond. The 3 infants who died of meconium-aspiration were delivered by cesarean section, the indication being

fetal distress; all 3 were found to have aspirated thick meconium. Two of these infants were delivered after 41 weeks of gestation, and the third was delivered after 42 weeks.

Comment

In this study meconium was found to be present in 10.7% of the infants delivered preterm. Matthews and Warshaw² did not find any meconium in patients at less than 34 weeks of gestation, but Parida⁸ found meconium in 3.7% of such cases. Ostrea and Naqvi⁹ found a 2.6% incidence in their preterm patients. Green and Paul¹⁰ found a 6% incidence between 29 and 36 weeks of gestation, and in 8% of their patients prior to 29 weeks' gestation.

In our study, spectrophotometric analysis used to document the presence of meconium in the amniotic fluid could account for the higher percentage of preterm patients positive for the presence of meconium. Although meconium was found in 10.7% of preterm patients, the incidence of meconium-aspiration in the infants delivered remained at a low of 0.5%. A significant increase in the presence of meconium was documented at 39 weeks' gestation. This increase at 39 weeks also has been reported by Eden¹ and Green¹⁰ and represents a normal physiologic indicator of fetal maturation¹¹ or compression of the cord in the mature fetus¹².

The impression that the presence of meconium alone, in the absence of any other risk factors, is a normal result of fetal maturation can be supported by the uneventful outcome of the majority of fetuses delivered despite the presence of meconium as reported in all studies¹⁰.

The significant increase in meconium at 39 weeks documented in our study was not accompanied by an increase in the meconium-aspiration syndrome until 41 weeks of gestation had been reached. This appears to confirm the finding that meconium alone is not a good predictor of adverse fetal outcome¹³; other factors besides the presence of meconium must be taken into account.

When fetal asphyxia is associated with meconium, it appears that the potential for perinatal morbidity and mortality is increased^{14,15}. Miller has suggested that fetal asphyxia with the presence of meconium can increase the potential for meconium-aspiration and poor neonatal outcome¹⁶. Grausz and Heimler reported that 5% of infants who died of unexpected asphyxia did so prior to 40 weeks' gestation, compared to 32.5% at 40 to 41 weeks and 37.5% after 41 weeks¹⁷. A similar gestational age distribution was found in their neurologically affected group of infants which led to the conclusion that pregnancies beyond 40 weeks require meticulous assessment of fetal well-being both before and during labor because this is the most frequently observed time for unexpected asphyxia¹⁷.

A decrease in amniotic fluid appears to be another factor in the meconium-aspiration syndrome. Amniotic fluid volume remains relatively constant until the 37th week of gestation; it declines gradually until the 40th week. After 40 weeks, amniotic fluid diminishes rapidly in a certain percentage of patients; the lowest amniotic fluid volumes are found at 41 weeks' gestation or later¹⁸. Of greater importance, is Clement's report that amniotic fluid volume could decrease significantly in less than 24 hours in post-dated pregnancies¹⁹.

Based on these studies, it appears that the fetus beyond 40 weeks with meconium in the amniotic fluid and oligohydramnios in the mother is at very high risk for developing unexpected fetal asphyxia. The decrease in volume can lead to the

TABLE 1: Gestational Age, Meconium Staining of Amniotic Fluid and Meconium-Aspiration Syndrome

Gestational Age	Deliveries	Meconium Staining	Percentage Deliveries	Meconium Aspiration	Percentage Deliveries
28	60	11	18.3%	1	1.7%
29	37	3	8.1%	0	—
30	74	10	13.5%	0	—
31	69	8	11.6%	0	—
32	119	15	12.6%	1	0.8%
33	138	12	8.7%	0	—
34	191	20	10.5%	3	1.6%
36	474	44	9.3%	1	0.2%

TABLE 2: Gestational Age, Meconium Staining of Amniotic Fluid and Meconium-Aspiration Syndrome

Gestational Age	Deliveries	Meconium Staining	Percentage Deliveries	Meconium Aspiration	Percentage Deliveries
37	963	115	11.9%	1	0.1%
38	2,177	281	12.9%	7	0.3%
39	3,493	621	17.7%	9	0.3%
40	4,165	874	21.0%	22	0.5%
41	1,689	414	24.5%	21	1.2%*
42	518	151	29.2%	10	1.90%
43	84	20	23.8%	0	—

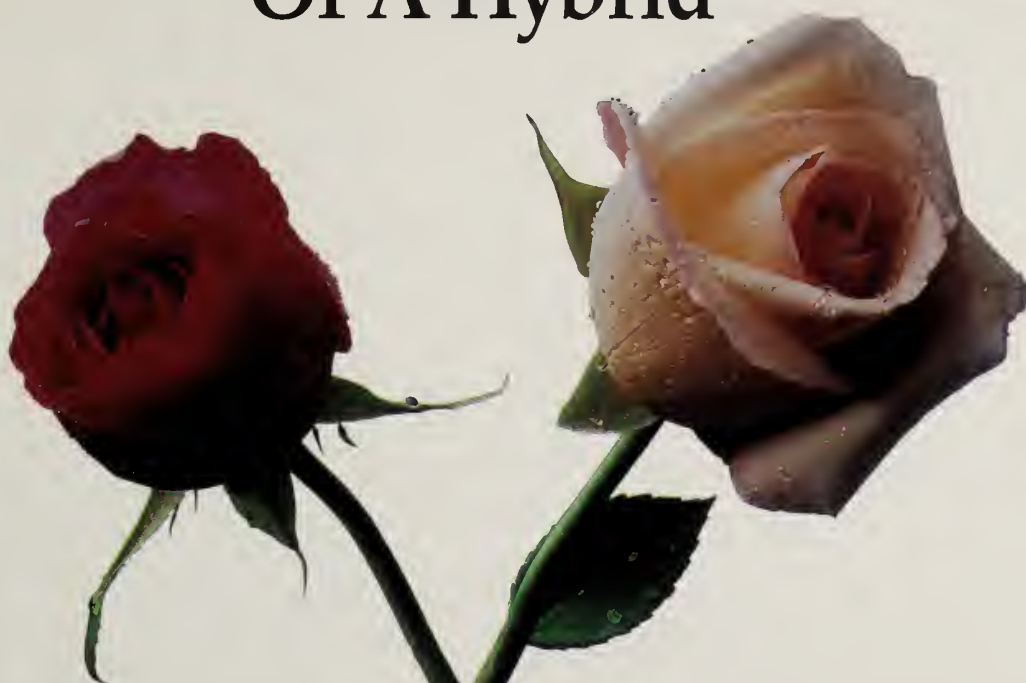
*P<0.005 between the current and previous weeks of pregnancy.

TABLE 3: Gestational Age and Meconium-Aspiration Syndrome in Patients with Meconium at Birth

Gestational Percentage	Meconium at Birth	Meconium Aspiration	Percentage
37	60	11	18.3%
38	37	3	8.1%
39	74	10	13.5%
40	69	8	11.6%
41	119	15	12.6%
42	138	12	8.7%
43	191	20	10.5%

**P<0.025 between the current and previous weeks of pregnancy.

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WARNINGS: General: *Enalapril Maleate; Hypotension.* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, Drug Interactions, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy (e.g., subcutaneous epinephrine solution 1:1000 0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided. (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis. Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Enalapril Maleate and Hydrochlorothiazide).

Pregnancy, Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses, 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality, below.)

Enalapril Maleate: Fetal/Neonatal Morbidity and Mortality. ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Premature, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no

alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide: Teratogenic Effects: Reproduction studies in the rabbit, mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-liter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Neonatal Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: General: *Enalapril Maleate; Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69[®]) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See Drug Interactions.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hyperkalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hyperkalemia. Hyperkalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see Drug Interactions, Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the

treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients: Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions, Enalapril Maleate: Hypotension—Patients on Diuretic Therapy: Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium. Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vitro* mouse

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bone marrow assay

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: re-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenetic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, by their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy: Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain, *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia, *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth, *Nervous/Psychiatric:* Nervousness, nervousness, paresthesia, somnolence, vertigo, skin: Pruritus, rash, *Other:* Dyspnea, back, back pain, arthralgia, diaphoresis, decreased libido, bruits, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, Cough.

Clinical Laboratory Test Findings: Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported. *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, Hemodialysis Patients); *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction; pulmonary edema, rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris, *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS); flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing. *Miscellaneous:* A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

Hydrochlorothiazide—Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions, *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

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meconium being thicker, which would make it more difficult for the trachea to be cleared at the time of delivery. Decreasing amniotic fluid volume also can lead to compression of the umbilical cord causing a further expression of meconium into the amniotic fluid. This would increase the likelihood of the in utero infant aspirating the meconium²⁰.

In our study, the incidence of aspiration of meconium remained at a relatively low level between 28 and 40 weeks of gestation. The incidence increased after 40 weeks' gestation and rose significantly at 41 weeks. All fetal deaths and 84% of the severe cases of meconium-aspiration in this study occurred at 41 weeks and beyond. In some centers, there is a trend to begin the induction of labor or surveillance of the fetus at the end of 41, and even 40, completed weeks because of a small number of unexplained stillbirths²¹. It appears that delivery prior to 41 weeks in a patient with oligohydramnios and the presence of meconium would significantly decrease the incidence of the most serious complications associated with the meconium-aspiration syndrome.

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A review of the anomalous origin of the left coronary artery from the anterior sinus of valsalva: Is prevention possible ?

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The origin of the left coronary artery from the anterior sinus of Valsalva is a rare coronary anomaly. Nevertheless, it remains an important pathological entity because of the possibility of its clinical and surgical consequences. Physicians should therefore be aware of this condition and consider it in their differential diagnosis of ischemic heart disease. This is a case report and review of the literature.

Introduction

The purpose of this paper is to provide an overview and to familiarize physicians with this anomaly. A review of 65 autopsies and cases of sudden death among these patients is included. In addition, we report a case of anomalous origin of the left coronary artery from the anterior sinus of Valsalva in Honolulu, Hawaii.

Case Report

An unmarried, 38-year-old Filipino woman was admitted to the hospital with a long-standing history of angina at rest and upon exercise. She had a history of diabetes, hypertension, and anemia; her only current medication was Nitrostat. Her past medical history included a tubal ligation in 1975 and two bladder infections, the last one in March 1990. Her family history was significant for sudden death—her mother died at age 45 of heart disease and the patient's child died at the age of 1 of an unknown cause.

Her blood pressure was 110/70, pulse 60 and regular, respirations 20, and temperature 98.7°C. The physical examination was otherwise unremarkable. Laboratory findings included a CBC, serum chemistries, serum electrolytes, and urinalysis were within normal limits. Echocardiography revealed mild cardiomegaly with left ventricular enlargement. The patient also had a positive thallium stress-test.

Angiography was performed to rule out coronary artery disease or an equivalent. It revealed normal left ventricular function and a large right coronary artery. There was a small left coronary artery arising from the right sinus of Valsalva that passed between the great vessels and provided primarily a circumflex distribution. (Figure 1: x-ray).

Surgical correction consisted of a coronary artery bypass graft. The left internal mammary artery was anastomosed to the left anterior descending coronary artery and a saphenous vein segment was used to connect with the circumflex system. The patient's postoperative course was uneventful with the exception of a single episode of low serum glucose (46 mg/dl). She was discharged 6 days later on Ecotrin and Persantine.



Figure 1: x-ray

Discussion

Normal coronary arteries have an architecture that is "...observed in at least 1% of unselected cases"¹. This definition allows for *normal variants*; therefore, any variation that occurs in less than 1% is an anomaly¹. The incidence of coronary anomalies has ranged from 0.28% to 1.2%²⁻¹⁰. Coronary anomalies can be divided into 3 categories:

- 1) Associated: A variation in response to a primary cardiac pathology.
- 2) Major: An abnormal coronary artery connection with a cardiac chamber or an abnormal origin from the pulmonary artery.
- 3) Minor: An abnormal origin from the aorta but with a normal distal circulation.

Anomalous origin of the left coronary artery from the anterior sinus of Valsalva fits into the third category. Its inci-

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dence has been reported between 0.02% and 0.19%^{2,3,4,9,11,12}. It is considered to be a minor anomaly because the blood entering both coronary arteries is fully oxygenated; this variation is compatible with life. However, numerous studies have documented that it is not such a benign condition after all. Cheitlin reported a 27% risk of sudden death in patients with this anomaly¹³.

The various routes an anomalous left coronary artery can take will be discussed prior to addressing possible mechanisms of these sudden deaths.

There are 4 pathways an anomalous left coronary artery can take as it travels from its origin in the sinus of Valsalva to its final destination by dividing into the left anterior descending and circumflex arteries. The first is known as the retroaortic pathway (Figure 3). The left coronary artery leaves the anterior sinus of Valsalva and courses posteriorly around the aorta to its normal distribution. Presently, no cases of sudden death in patients with this pathway have been reported. In addition, Murphy reported a myocardial infarct over the distribution of the left coronary artery in one such patient. Symptoms were alleviated with bypass surgery of the anomalous left coronary artery although both coronary arteries were devoid of atherosclerosis¹⁴. This strongly suggests that the ischemia was caused by the retroaortic anomaly.

The second course an anomalous left coronary artery can take is called the anteropulmonic pathway (Figure 4). The left

coronary artery leaves the sinus of Valsalva and travels anteriorly to the pulmonary artery to its normal distribution. Roberts reported sudden death in one such patient¹⁵. Pachinger presented a patient with such an anomalous left coronary artery who had angina despite patent coronary arteries¹⁶. Chaitman reported myocardial infarction in the left coronary artery's distribution in another patient with patent coronary arteries². These studies of ischemia in the presence of patent but anomalous coronary arteries point to the possible cause of sudden death. Roberts and Kragel also reported sudden death in one such patient¹⁵. This evidence indicates that the anteropulmonic route of an anomalous left coronary artery is not a benign condition.

The third course is known as the interarterial pathway, in which the left coronary artery courses between the aorta and pulmonary artery (Figure 5). This is the most hazardous form and is responsible for a vast majority of the sudden deaths attributed to an anomalous left coronary artery from the anterior sinus of Valsalva.

There is a fourth, benign type of anomalous left coronary artery that has a septal pathway (Figures 6 and 7). The left coronary artery leaves the aorta and burrows into the ventricular septum, and it emerges anteriorly to branch into the left anterior descending and circumflex arteries which follow their usual courses. In a review of the literature, there has been only one

(Continued) ➤

Legend : All superior views

- CX - Circumflex
- LAD - Left Anterior Descending Artery
- LMC - Left Main Coronary Artery
- RCA - Right Coronary Artery
- PA - Pulmonary Artery
- LSV - Left Sinus of Valsalva
- RSV - Right Sinus of Valsalva

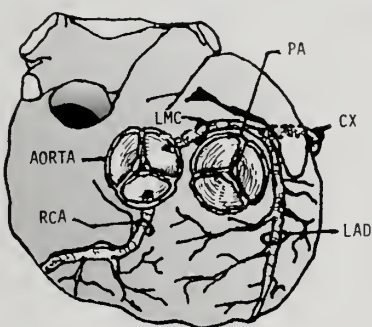


Figure 2: Normal anatomy of the coronary arteries.

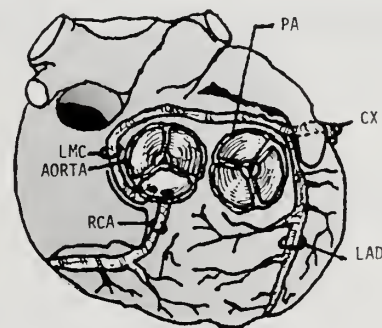


Figure 3: Anomalous left main coronary artery coursing posterior to the aorta.

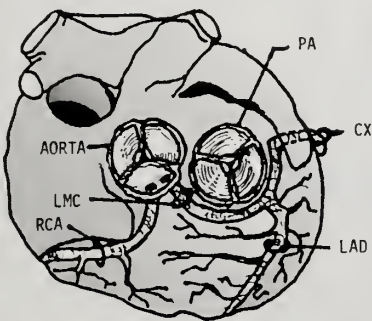


Figure 4: Anomalous left main coronary artery coursing anterior to the pulmonary artery.

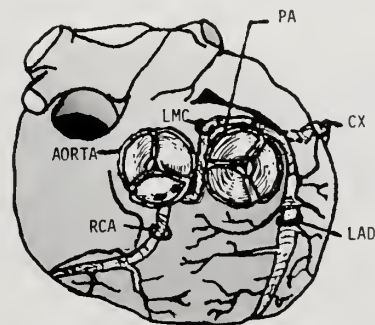


Figure 5: Anomalous left main coronary artery coursing between the aorta and pulmonary artery.

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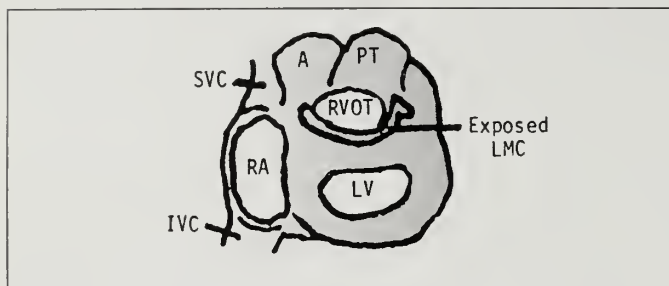


Figure 6: Transverse section through heart showing anomalous LMCA coursing in the ventricular septum view from below..

Figure 6 legend

A	—	Aorta
PT	—	Pulmonary
SVC	—	Superior Vena Cava
IVC	—	Inferior Vena Cava
LMC	—	Left Main Coronary Artery
CX	—	Circumflex Artery
LAD	—	Left Anterior Descending Artery
RVOT	—	Right Ventricular Outflow Tract
RA	—	Right Atrium
RV	—	Right Ventricle
LV	—	Left Ventricle

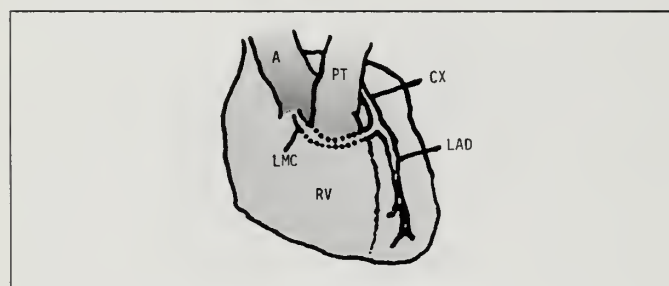


Figure 7: Anomalous left main artery coursing in the ventricular septum (anterior view).

patient documented with this septal pathway which might have contributed to his death¹⁷. This condition is considered to be relatively benign, and patients with the septal route typically live to advanced ages.

There has been much speculation as to the exact cause of sudden death in patients who have anomalous left coronary arteries originating from the anterior sinus of Valsalva. Most cases have been directly related to exercise. Of 39 cases of sudden death in patients under the age of 30 reviewed in the literature, 34 were exercise-related.

The most popular theory is that the anomalous coronary artery is compressed between the aorta and pulmonary artery during exercise^{3,18,19,30}. Ischemia could be caused by the unsatisfied need for increased oxygen consumption by the myocardium and in peripheral vasodilation, or by an increase in systolic pressure leading to compression of the anomalous coronary artery.

Murphy¹⁴ documented a case in which the density of contrast medium in the anomalous left coronary artery clearly diminished during systole.

This explains why sudden death almost never happens in patients with an anomalous septal left coronary; the buried left artery might be protected from compression.

Cheitlin disagreed with the compression theory and said that the pulmonary artery, a low-pressure system, would be an unlikely candidate in the compression of the left coronary artery¹³. However, patients with normal right ventricles and pulmonary vasculature have been found to develop marked transient pulmonary hypertension both before and after a coronary bypass operation¹¹. Corday and associates have found that pulmonary hypertension can compress the coronary arteries²⁰. Thus, transient pulmonary hypertension with a physiologic increase in systolic blood pressure during exercise could compress the anomalous left coronary and hinder its flow.

Several authors have discovered atherosclerotic stenosis in the portion of the anomalous left coronary artery that passes between the aorta and pulmonary artery. These plaques were postulated to be the result of chronic compression^{7,19}. This is unlikely to be the sole cause of sudden death, but in conjunction with left coronary artery compression could compromise coronary blood flow.

Another theory based on ischemia deals with the acute angle

SURGICAL APPROACH

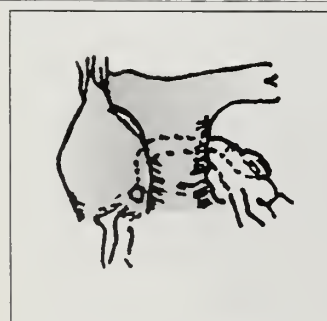


Figure 8a: Anomalous LMC

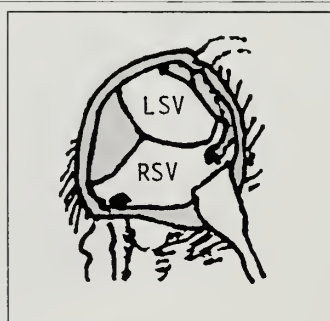


Figure 8b: Exposure of the anomalous LMC

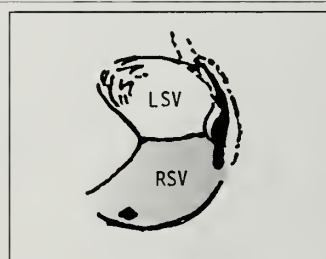


Figure 8c: The ostium is split and the incision is extended above the intercoronary commissure until the midpoint of the left coronary.

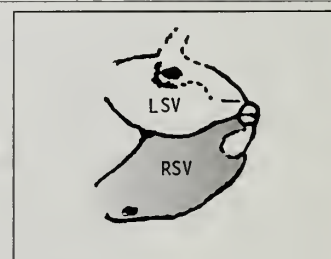


Figure 8d: The intima of the LMCA and aorta are joined, and the inter-coronary commissure is reattached

present in many cases as the artery leaves the aorta. An acute angle can be defined as an angle of less than 45 degrees between the aorta and the proximal portion of the left coronary artery²¹. Several authors have noted that an acute angle could lead to luminal narrowing and reduced myocardial blood supply from luminal kinking and intramural stretching as cardiac output and pressures are elevated during exercise^{3,7,13,19,22}. Virmani, in a study of sudden death victims, found a significant increase in the incidence of such acute angles when compared with a control group²¹; acute angles were present in 18 of the cases reviewed²¹. A slit-like ostium was commonly found in association with an acute angle of the anomalous left coronary artery, often in conjunction with a flap-like closure. This condition was found in 11 of the cases reviewed, 10 of which possessed an acute angle. The already narrowed ostium could be narrowed further with exercise as the aorta distends, reducing coronary blood supply.

In addition, several authors have reported that the proximal left coronary artery that exits the ostium travels within the wall of the aorta, sharing a common intima^{23,24}. With exercise, the aorta dilates, and as Sacks proposed, the intramural portion becomes flattened, reducing blood flow²³.

Virmani also described ostial ridges (defined as a ridge whose surface area occupied 50% of the coronary ostial area). In his study, 22 sudden death victims were compared with a control group of 19 patients who died of known causes. All 41 hearts were examined for abnormalities such as acute angle takeoff and ostial valve-like ridges. Patients with the anomalous left coronary artery with origin from the anterior sinus of Valsalva had a significantly higher incidence of ostial ridges than their control group counterparts. The ridges were thought to impede flow by compressing the left coronary artery as the aorta dilated during exercise²¹.

Another possible cause for ischemia is congenitally hypoplastic coronary arteries. This is not the sole factor leading to sudden death in patients with anomalous left coronary arteries because only 5 of the cases possessed a left coronary artery significantly smaller than the

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right coronary artery. However, all 5 of these cases were associated with sudden death.

A final possible mechanism is coronary vasospasm. Maddoux and associates documented a single case of coronary vasospasm in an anomalous left coronary artery that led to myocardial ischemia²⁴.

It is important to keep in mind that all of these theories could be valid. Sudden death in patients with anomalous left coronary arteries cannot be explained by any one element alone; all of the aforementioned theories might play a role. The final pathway from ischemia to sudden death is commonly ventricular fibrillation²⁵.

It is essential to evaluate any patient with chest pain unattributable to typical causation because of the possible presence of a precarious anomalous left coronary artery. A workup needs to include a base ECG and a radionuclide-scanning exercise stress test to locate regional perfusion deficits. In several cases, this has been helpful in revealing an anomalous left coronary artery²⁶. However, several authors have reported myocardial infarction/sudden death in patients with anomalous left coronary arteries despite previous negative exercise stress tests^{14,27,28}.

Although anomalous left coronary arteries have been identified by echocardiography, angiography eventually will be necessary for a definitive diagnosis^{7,26}. It is essential to define the exact course of the anomalous left coronary artery for both prognostic and surgical reasons. There are 3 components of direction in an anomalous vessel: Sagittal, transverse, and coronal planes. Therefore, 2 views are necessary during angiography; the 2 most informative views are the right anterior oblique and the lateral projections²⁹.

The symptomatic young adult with an anomalous left coronary artery is of primary concern, whereas the same condition in adults is far less likely to result in sudden death. However, it is recommended that all patients undergo surgical correction. A thallium exercise-stress test should be performed. If positive, the anomalous vessel should be bypassed. However, if negative, the patient should be followed over time (Figure 8)²⁶.

The surgical alternatives are: Ostioplasty, separate coronary artery bypass grafting (CABG) to the left anterior descending and circumflex arteries, CABG to the left coronary artery and relocation of the ostium. Enlarging the ostium should be attempted only if the ischemia involved with an anomalous left coronary artery was caused by the slit-like ostium and the acute angle takeoff of the vessel. If the mechanism of ischemia is compression between the great vessels, such an operation would be ineffective. In a review of the literature, there were 3 documented cases of ostioplasty^{13,32,33}. In each case, the patients improved postoperatively. In one of the cases, there was a 7-year follow-up on the patient which corroborated the success of the procedure.

Treatment with bypass grafting has received equal success. Sacks used a single graft to the left coronary artery and said this procedure would cause less restriction of flow than to apply separate grafts to the left anterior descending and circumflex arteries²³. Nevertheless, there also have been many cases of separate bypass grafts that were extremely successful in alleviating symptoms of myocardial ischemia^{7,11,24,26,29,33,34,35,36,37}. These results suggest that compression of

the anomalous left coronary artery plays a significant role in myocardial ischemia.

Mustafa and colleagues suggest an innovative alternative²². The ostium of the left coronary artery is incised and separated from the anterior sinus of Valsalva and the incision extended to above the intercoronary commissure up to the midpoint of the left coronary sinus. At this point, the intima of the left coronary artery and the aorta are joined and the intracoronary commissure reattached to the aorta (Figure 8). That patient did well postoperatively with a normal cardiac catheterization at 1- and 2-year follow-ups²². This procedure also was performed by Donaldson and associates with similar results⁹.

Despite the success of these surgical techniques, it is difficult to judge which procedure is superior. There are no long-term follow-up results. The theoretical efficacy of one operation as compared to another would depend on which theory of the causation of ischemia in anomalous left coronary arteries was correct. The success of various surgical procedures supports the possibility that the ischemia could be caused by a combination of factors.

The ideal remedy would be primary prevention. This concept might appear to be far-fetched; however, as a result of significant advances in embryology and early detection of this anomaly, a preventive modality might loom. The first step toward achieving prevention must lie in understanding how the coronary arteries are formed and what circumstances can result in anomalies. If the causes of coronary anomalies can be discovered and techniques for predevelopmental detection developed, it is quite possible that someday such anomalies might be prevented.

Conclusion

Anomalous origin of the left coronary artery from the anterior sinus of Valsalva can be a serious entity that must be kept in mind in the differential diagnosis of any chest pain otherwise unexplainable. The anomaly is important in terms of the surgical implications, despite its rare occurrence. A high index of suspicion, a correct diagnosis and prompt surgical intervention could prevent sudden death. It is hoped when the embryology of coronary arteries and the causation of anomalies become understood in greater depth, a cost-effective means might be developed for the in-utero detection and prevention of these anomalies.

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Sugarcane workers: Morbidity and mortality

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Sugarcane is, after pineapple, the largest agricultural industry in Hawaii. There have been reports that this industry poses certain health hazards. To investigate this possible hazard in Hawaii, the relationship of employment on a sugarcane plantation to total mortality, the development of definite coronary heart disease (CHD), stroke, cancer, lung cancer and certain risk factors were examined in men of Japanese ancestry participating in the Honolulu Heart Program. After 18 years of follow-up, those men who indicated one or more years working on sugarcane plantations had no significant difference in age-adjusted mortality, nor incidence of CHD, stroke, cancer, or lung cancer. There were no differences in risk factors compared to participants who were never employed on sugarcane plantations, nor were there differences in lung function as measured by FEV₁. These findings were unchanged after adjusting for several potential confounding variables. No cases of mesothelioma were observed among those with a history of defined exposure. These findings were not due to a "healthy worker bias" and indicate that employment on a sugarcane plantation in Hawaii is not associated with elevated rates of chronic diseases.

Introduction

Prior data on the occupational risks of employment on sugarcane plantations have not been subject to much research. There is a defined occupational pneumoconiosis, bagassosis, that is known to occur among those who work with or around moldy bagasse (the remnants of sugarcane after sugar extraction)^{4,5}. Das et al³, Gottlieb et al⁶, and Rothschild and Mulvey¹⁴, have reported either lung cancer or mesothelioma among sugarcane plantation workers. Steineck et al¹⁶ found increases in mesothelioma in sugar refinery workers.

In Hawaii prior to harvesting, growing sugarcane is burned to reduce leafage and improve sugar recovery. Newman^{10,12} has identified fibers in the smoke from sugarcane that resemble asbestos fibers. His findings imply that those exposed to sugarcane smoke during the routine burning and harvesting of sugarcane fields can be at greater risk of lung cancer, mesothelioma or pneumoconiosis.

The objective of our study was to investigate the possible relationship between working on a sugarcane plantation and the inci-

dence of definite coronary heart disease (CHD) cancer. We also sought a possible relationship between this occupation and risk factors using the cohort from the Honolulu Heart Program (HHP).

Methods

Defining of the study population

The HHP cohort was first established in 1965 and was comprised of men of Japanese ancestry born between 1900 and 1919 who were residents of Oahu at the time of the baseline examination. Between 1965 and 1968, 8,006 men participated out of the 11,148 who were known to be eligible as identified in the World War II Selective Service list.

Occupational classification

Prior to the first examination letters were sent to each subject person explaining the study and asking certain questions. Some of these questions referred to employment. There were 9 employment categories, one of which was "sugar industry". This information was coded.

At the baseline examination, an interviewer asked each participating member of the cohort what was his present and his usual occupation and how many years he had been employed in each job. Specific questions were asked as to whether he worked in the field or elsewhere. The duration of sugar plantation employment was recorded at a third follow-up examination 6 years after the baseline examination.

A plethora of occupational information was therefore available for analysis. Two occupational variables showed up: The first variable included all those working at least one or more years on sugarcane plantations (n=2537). There was a total of 5,300 individuals in the cohort about whom this information existed. The second variable was our stratification of the first according to the number of years worked; zero (did not work on the sugarcane plantations), 1 to 5 years, 6 to 10, and 11+ (n=2763, 1903, 422 and 212 subjects respectively). Data on specific job activity within the sugarcane plantations were not available.

Risk factors

At the initial examination of the persons in the cohort measurements of blood pressure, FEV₁, body mass index (kg/height in m²=square meters) and serum cholesterol were made on each participant.

The interviewer also inquired about smoking habits and alcohol consumption. Smoking was recorded as the number of cigarettes per day times the number of years smoked, converted to cigarette-years. The number of ounces of ethanol per month was estimated using conversion factors as specified in *USDA Handbook No. 8*¹⁷.

Outcomes and diagnostic criteria

Prevalent cases of definite coronary heart disease, stroke and cancer were identified at baseline. Of the 8,006 men examined

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at baseline, 456 had existing disease and were excluded from follow-up. This left 7,550 men for follow-up, of which 1,824 had died by December 31, 1987. Data on specific cause of death and incidence of fatal and non-fatal CHD, stroke and cancer were available over an 18-year follow-up period.

Ascertainment of morbidity and mortality was obtained from 2 additional follow-up exams completed 2 and 6 years after the first exam and by a comprehensive surveillance system of hospital discharge records on the island of Oahu¹⁸. The cause of death of all HHP members was determined by consensus of a panel of study physicians.

The definition of CHD included non-fatal myocardial infarction, CHD death and sudden death within 1 hour. Thromboembolic or hemorrhagic stroke as defined by a neurologist in the panel was based on clinical, surgical and/or autopsy findings. In addition, cancer incidence was determined by a review of new tumor accessions at the Hawaii Tumor Registry. Thus data on causes of death and incidence of cardiovascular disease and cancer were available for an 18-year follow-up period.

Statistical analyses

Life table analyses were employed to estimate comparative incidence rates of CHD, stroke, cancer and total mortality. All comparisons between the "exposed" and not "exposed" were adjusted for age and, when appropriate, for other risk factors such as alcohol and smoking by a covariance method using a proportional hazards model². Estimates of the mean of risk factors in categories of occupation were also compared and adjusted for age by the covariance method, using standard ANOVA models.

Results

Table 1 shows the results in age-adjusted mortality rates for each of the 2 occupational variables. There was no significant increase in risk among those working 1 year or more on sugarcane plantations nor was there any significant pattern with increasing years of work on sugarcane plantations in terms of total mortality.

The incidence of relative risk of definite CHD and of mortality because of working on sugarcane plantations were very close to 1, as shown in Table 2. None of the 95% confidence intervals showed relative risk significantly different from unity. Similar patterns can be seen in Tables 3, 4, and 5 in stroke, total cancer and lung cancer respectively. There were no mesothelioma cases among any of those occupations defined as sugarcane workers.

Some occupations can be linked to the risk of chronic diseases indirectly through risk factors such as blood pressure, serum cholesterol, body mass, tobacco, alcohol consumption and lung function. The changes in these risk factors can be more sensitive predictors of exposure to airborne particulates generated during sugarcane cultivation and harvesting than incidental disease.

The results in comparing risk factors and sugarcane plantation employment are shown in Table 6. The age-adjusted values by employment-variables were essentially the same. The sugar workers did have a slightly better FEV₁, but this was not statistically significant. The mean FEV values were adjusted for the degrees of cigarette smoking. This did not change the results; the smoking habits were not significantly different between the sugar plantation workers and non-plantation workers.

These results indicate that those who had worked on sugar plantations experi-

enced similar rates of the most common chronic degenerative diseases as compared with non-plantation workers. However, most of the cohort had quit working on plantations by the time of the first examination in the late 1960s. It is possible, though unlikely, that those working on sugar plantations took jobs that were associated with low chronic disease rates and mortality, and those who never worked on plantations had taken jobs later that were associated with high rates of chronic disease and mortality. In order to address this possible bias, a frequency table of occupations at the first examination was generated to see if the sugarcane workers had preferentially selected one or more occupations.

The list of occupations has more than 400 titles and therefore is not included here. No meaningful difference in the distribution of occupations selected by the 2 groups was found. Differences in frequencies between sugar and non-sugar workers for a given occupational title were never greater than 3 percentage points. This suggests that occupations taken after working on the sugar plantations did not project a bias on the observed rates compared above.

A more specific analysis was done using the occupational classification of carpenters. We knew this was the most frequently recorded occupation in the cohort⁹. The HHP carpenters had lower CHD rates and total mortality as compared to the overall rates in the cohort. Those classified as having one or more years working on sugarcane plantations were cross-tabulated by carpentry. The cross-tabulation showed that the sugarcane workers did not preferentially select this occupation compared to the non-sugarcane workers.

Discussion

No association between sugarcane plantation employment and increased risk of CHD, stroke, cancer, lung cancer, or of total mortality was found. There were no mesothelioma cases among sugarcane workers. Moreover, the risk factors for these diseases were not elevated in the sugarcane plantation employees. Lung function results were similar to those who did not work on sugarcane plantations and did not indicate any trend to decrease with the duration of employment on the plantations. Furthermore, there was no evidence that work in other occupations could have accounted for these results.

There are several factors that influence the interpretation of these results. These factors are discussed below.

Bias due to misclassification of disease was minimized by the protocol for diagnosis in the project. Loss to follow-up was minimized by an effective surveillance system for identifying incident cases¹⁸.

The groups for comparison were taken from the sub-populations of the HHP cohort; they were ethnically homogenous. This minimizes one of the problems in selecting comparison groups

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Bea Okuda
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in occupational epidemiology. The removal of existing cases of chronic diseases at the time of baseline examination further reduces possible differences between the exposed and non-exposed groups and eliminates the "healthy worker" (HW) factor. The HW factor skews the findings when the comparison groups are taken from the general population which includes both healthy and diseased individuals.

The sugarcane industry population is ethnically heterogeneous. Through the 1920s to the 1950s the sugar plantation working population has been approximately 22% Japanese⁹. The proportion of the working Japanese male populations on the different island plantations ranged from 17% to 25%. Almost 80% of the employees currently are from other ethnic groups, primarily Filipino. Our study was not designed to cover the health status of these other employees.

The data do not include the names of the sugarcane plantations or their locations. Therefore in the case of any given individual HHP cohort member, the sugarcane plantation where he was employed is not given. As mentioned above, all cohort members were residing on Oahu when the study began in the late 1960s. This indicates that the plantations were on Oahu. Hawaii Sugar Planters Association (HSPA) records show there was no significant difference in operations between the sugar plantations and the working conditions for their employees on the several islands of Hawaii (Whalen S, Archives of the Hawaii Sugar Planters Association. Personal communication. 1989).

It is unlikely that all the Japanese employees in the sugar industry had the same job description or that all Japanese employees worked in the field or were blue-collar workers.

TABLE 1: Age-Adjusted Rates per 1000 for Total Mortality during the Surveillance Period from 1956 to Dec. 31, 1987

Years Worked	N	RR	95%	CI	Rate/1000
1 or more					
Yes	2537	0.98	0.87	1.10	119.2
No	2763	1.00	0.00	0.00	121.6
0 to 11+					
0	2763	1.00	0.00	0.00	121.6
1 - 5	1903	0.99	0.87	1.12	120.4
6 - 10	422	0.95	0.75	1.20	115.7
11+	212	0.95	0.71	1.27	115.9

TABLE 2: Age-Adjusted Rates per 1000 for Definite CHD and Mortality for Surveillance Period from 1956 to Dec. 31, 1987

Years Worked	N	RR	95%	CI	Rate/1000
1 or more					
Yes	2537	1.09	0.91	1.30	85.5
No	2763	1.00	0.00	0.00	78.8
0 to 11+					
0	2763	1.00	0.00	0.00	78.8
1 - 5	1903	1.11	0.92	1.34	86.8
6 - 10	422	0.94	0.66	1.35	74.4
11+	212	1.22	0.80	1.85	95.2

TABLE 3: Age-Adjusted Rates per 1000 for Stroke and Mortality for the Surveillance Period from 1956 to Dec. 31, 1987

Years Worked	N	RR	95%	CI	Rate/1000
1 or more					
Yes	2537	1.08	0.85	1.36	44.1
No	2763	1.00	0.00	0.00	41.0
0 to 11+					
0	2763	1.00	0.00	0.00	41.0
1 - 5	1903	1.06	0.82	1.37	43.6
6 - 10	422	1.24	0.80	1.91	50.6
11+	212	0.92	0.49	1.69	37.6

TABLE 4: Age Adjusted Rates per 1000 for Total Cancer and Mortality for the Surveillance Period from 1956 to Dec. 31, 1987

Years Worked	N	RR	95%	CI	Rate/1000
1 or more					
Yes	2537	0.97	0.84	1.12	115.2
No	2763	1.00	0.00	0.00	118.6
0 to 11+					
0	2763	1.00	0.00	0.00	118.6
1 - 5	1903	0.95	0.81	1.12	113.4
6 - 10	422	0.96	0.72	1.28	114.3
11+	212	1.12	0.80	1.58	132.2

TABLE 5: Age Adjusted Rates per 1000 for Lung Cancer and Mortality for the Surveillance period from 1956 to Dec. 31, 1987

Years Worked	N	RR	95%	CI	Rate/1000
1 or more					
Yes	2537	1.26	0.89	1.78	19.0
No	2763	1.00	0.00	0.00	15.1
0 to 11+					
0	2763	1.00	0.00	0.00	15.1
1 - 5	1903	1.23	0.85	1.78	18.5
6 - 10	422	1.13	0.56	2.28	17.1
11+	212	1.80	0.86	3.78	27.1

TABLE 6: Age-Adjusted Risk Factors, Mean Values for the Surveillance Period from 1956 to Dec. 31, 1987

Years Worked	N	Cholesterol	SBP	FEV ₁ *	Cig/Year	Alcohol	BMI
1 or more							
Yes	2537	218.1	132.9	2.74	457.9	13.1	24.1
No	2763	217.7	133.2	2.72	451.0	13.8	23.7
0 to 11+							
0	2763	217.7	133.2	2.72	451.0	13.9	23.7
1 - 5	1903	218.1	132.7	2.74	463.3	13.5	24.1
6 - 10	422	217.8	133.5	2.73	446.8	13.0	23.9
11+	212	221.6	132.8	2.74	431.6	10.5	24.4

*FEV₁ was adjusted for height and cigarette years.

Industry records suggest the Japanese employees were most likely blue-collar field or plant workers rather than white-collar office workers (Whalen S). Blue-collar or white-collar occupational status has not been found to be associated with CHD, stroke, cancer, total mortality or the related risk factors in the HHP cohort (unpublished data).

Only a few of the employees on a sugarcane plantation are exposed directly to sugarcane smoke, which is the primary source for the fibers described by Newman^{10,12}. On a given plantation there are usually 1 to 4 employees trained to burn sugarcane fields. These individuals almost always set the fires with the wind at their backs, which means the wind blows the smoke away from the worker. In a given field of 40 to 60 acres, the sugarcane leaves are burned off in 20 to 40 minutes and the fire burns out in less than an hour. Although more than one field can be burned daily, the period of exposure is brief and involves a very small group of the overall plantation personnel. Exposures to other field workers have not been notable.

However, other field employees could be potentially exposed to a variety of environmental and occupational hazards. The classifications of sugarcane-plantation employment does not provide specific information as to job description, whether the employee worked indoors or outdoors, or any specific information that would specify the degree of exposure. This would tend to dilute an association, especially a weak association, resulting in a false negative conclusion. In addition, individual participants could have incorrectly reported their occupational history although each participant was asked directly by an interviewer if he was or had been working on sugarcane plantations and for how long.

Exposure was defined according to job duration in years and had a skewed distribution, ie, most of these employees were exposed for only a few years, and few employees were exposed for long periods. The analysis based on job duration did not show any particular trend in any of the outcome variables, suggesting that longer observation would not have provided any further insight. The statistically insignificant trend in lung cancer, however, warrants some measure of uncertainty in the conclusion and could justify the need for additional observations. The relative risk was very low even in the group with the highest exposure. The attributable risk, ie, the proportion of cases in the exposed group that could have had an adverse consequence prevented by removing the exposure, thus reducing the impact on public health, is small.

Bagassosis has been reported in many sugarcane-growing areas^{4,5,8}. There have not been any cases of this pneumoconiosis reported in the Hawaii sugarcane industry, however. The results of the lung function tests suggest little if any pneumoconiosis occurred among HHP cohort members working on the sugarcane plantations, compared to those working elsewhere. The actual number of employees on Hawaii sugarcane plantations working with bagasse are small, probably less than 20 persons. Individual cases of pneumoconiosis, however, could have been missed.

Rothschild and Mulvey¹⁴ reported an odds ratio of 2.4 for lung cancer on sugarcane farms in Louisiana after adjusting for smoking tobacco. The authors couched their conclusions with numerous caveats. Their hypothesis was generated by analysis of data; their interviewers were not blinded; their study was retrospective in design, and a specific causal agent was not identified. In addition, non-participation was at a rate of nearly 30%; possible selection bias in

controls was not addressed; there was no clear dose response; their findings were not consistent with association of lung cancer and shipbuilding as has been reported in Louisiana and elsewhere^{1,6,7,13,15}; and the 2 mesothelioma cases reported in the sugarcane farmers can be explained on the basis of chance. Perhaps most important, their report did demonstrate that the sugarcane farmers worked in sugar refineries or were otherwise exposed directly to sugarcane smoke.

Previously, Gottlieb et al⁶ had completed an investigation in southern Louisiana and reported that excesses in lung cancer were related to the manufacture of transportation equipment, mainly in shipbuilding and the fishing industry. Steineck et al¹⁶ attributed the excess in mesothelioma to asbestos in sugar refinery workers and not to organic fibers in dust. This suggests that exposure to asbestos could explain the excess lung cancers. Our results are not consistent with those reported by Rothschild and Mulvey¹⁴ or those reported by others that indicate increased risk of lung disease or dysfunction^{3,10,12}.

In conclusion, the studies needed to investigate further the hazards in sugarcane work will need more specific data on exposure and on the duration of exposure over longer periods of time. Ideally, exposure data are needed based on inhalation of actual toxins by individual workers. A population defined by such exposures will need to be followed over a long time in order to determine the effects on health that could result from such exposures.

Acknowledgement

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Endarterectomy and shunt: Alternatives or in tandem?

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There is no doubt about the efficacy of endarterectomy in the instance of localized occlusions of the arterial tree. The procedure was first developed in 1946 and has been widely used. However, in the case of extensive, non-localized atheromatous disease of the aorta-iliac and the femoral-popliteal-tibial segments in the leg, the majority of vascular surgeons prefer the application of shunts or prosthetics. Nevertheless, there are proponents of extensive obliteration of the endothelium in these regions. There is also the possibility of combining both techniques.

In order to assess the outcomes of the latter technique, we reviewed 567 patients who were operated on for aorta-iliac and for femoro-popliteal-tibial disease at Chelyabinsk Centre for Vascular Surgery in Russia from 1987 to 1991.

Five hundred forty-one of these suffered from atherosclerosis. The other 26 patients had non-specific inflammation of arterial system.

The age distribution was 32 to 78 years; there were 551 men and 16 women. Ischemia in the degree of III to IV (according to the scale established by Fontain) was present in 341 patients.

Multi-site occlusions and associated multi-organ disease affected 213 patients. Atheromatous disease was determined by ultrasonography, load tests and angiography.

Results

One hundred thirty-one femoro-popliteal and femorotibial shunt operations were performed. Of these, in 29 (22.3%) the patient developed thromboses in the early post-operative period because of the extensive disease in the tibial arteries. Twenty went on to require amputations and 4 of these amputations had to be performed in the presence of suppuration in the site when there was evidence of erosive bleeding. The mortality rate was 0.8% in this cohort.

Endarterectomy was performed on 149 patients with diseases in the same areas. Early thrombosis occurred in 35 patients (23.5%). Subsequent repeat endarterectomy was successful in 12 of these cases; however, amputations of the extremity had to be performed on 23 of the 35 as a last resort. The mortality rate was again 0.8% overall, but the causes were probably because of the severe concomitant organic disease in these cases.

An interesting fact in the instance of shunting the "blind" segment (the proximal part of only one of 3 collateral arteries being patent) in 8 patients, was that 4 of them developed thrombosis in 2 to 3 weeks post-op, resulting in amputations.

In 15 similarly afflicted patients on whom endarterectomy was performed, 3 required subsequent amputation; the remainder (12) had their arterial tree patent for anywhere from 2 to 5 years. To our mind, in such situations, endarterectomy enables the distal artery to remain patent longer.

Two hundred eighty-three patients were operated on for aorta-iliac occlusive disease; of these 143 had shunts and prosthesis. Thrombosis developed in 24 (16.8%) of these and 10 went on to require amputations. Suppuration occurred surrounding the pros-

thesis in 7 requiring removal of the prosthesis and amputation in two of the cases; in the other 5 patients a substitute of the prosthesis by an autologous vein segment resulted in a good outcome. Four patients died.

In this area of disease, 144 endarterectomies were performed; in 31 of these the approach was via the retroperitoneal space according to Rob. The results in 5 of these were immediately satisfactory as well as in follow-up.

The endarterectomy was performed transfemorally in 113 cases, utilizing the rings of Vollmar as a technique. Early thrombosis took place in 21 patients (14.6%) and 18 amputations had to be done. Two patients died. Such things as suppurations in the region, aneurysms at the suture sites and other complications attendant on the insertion of prosthetics were not noted in this cohort of patients.

Discussion

Actuarial assessment of the follow-up periods confirmed there was no great difference between the 2 techniques in terms of outcome. It is our opinion that the insignificant difference between the outcome of the 2 techniques is due less to the methods themselves than to the experience and skill of the surgeon, the appropriateness of the operating equipment and instruments available, and the extensiveness of the atheromatous occlusive disease.

We conclude, therefore, that both operative procedures are effective; they complement each other if in the hands of an experienced surgeon.

Shunting is the more common procedure and a relatively more simple method to remedy extensive occlusion of the arterial tree. Nevertheless, endarterectomy is more beneficial when the threat of intercurrent disease, such as diabetes and immunosuppression, compromises the likely success of a bypass procedure. The surgery is simplified and the survival of the patient more likely when endarterectomy via the transfemoral route is chosen in the case of multi-organ atheromatous disease being present.

Endarterectomy is more advisable hemodynamically when it is a matter of improving blood-flow into the "blind segment". It can be performed as a first stage procedure; if it fails because of the extent of the occlusive process, then shunting as a second stage is warranted.

Editor's note

We present this article to our readers as an example of what the Russian surgeons in Siberia have been doing during the period of Glasnost and Perestroika—the Gorbachev era. Remarkably, during the 70+ years of the prior Communist dictatorship, such reports were stifled.

In this instance, there was the additional problem of communication between Hawaii and Russia during the post-Gorbachev era—when the infrastructure of the erstwhile Soviet Union has broken down and no effective social structure has as yet ensued to take its place. The example, of course, is in the difficulties we had with the mail, the telephone and facsimile. The article above is as it finally evolved; a Russian physician trying to write in broken English meant that we had to go to-and-fro many times in order to clarify things.

(Continued on page 306) ►

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All the news that can be created. "I had my TV antenna removed. It's the moral equivalent of a prostate operation."

NBC's prime time newsmagazine, "Dateline NBC," was obliged to make an unprecedented on-air apology for the incendiary device hoax, which portrayed a Chevrolet pick-up bursting into flame in a collision. Now a similar apology is being demanded by the Southeastern Eye Center in Greensboro, NC. An undercover NBC volunteer was clearly told twice by a doctor that she did not need cataract surgery, but when a technician appeared to give conflicting advice, the patient scheduled surgery anyway. NBC claimed the patient was only one-half hour from the operating room before the network stepped in. The Southern spokesman stated that the patient would have been caught in the final safety net and surgery would not have occurred. The TV show was condemned by many sources for its unfair presentation, while the eye center suffered a 30% drop in business. The NBC producer, Neal Shapiro, claims the story was fair, but apparently there was dissent on the staff about including the Southeastern incident. However, integrity in television is irrelevant—ratings are the issue!

Good news—Bad news

◆ Good news—Surgeons are due a 12.2% Medicare increase in 1994 because actual volume in 1992 fell short of targets. Bad news—HCFA reduced the figure to 3.6%.

◆ Good news—OBRA 93 restores pay equity for new physicians. Bad news—the Justice Dept. is prosecuting even unwitting offenders who exceed billing limits.

◆ Good news—Optical shops were removed from the list subject to self-referral ban. Bad news—IOL payment will be reduced from the current \$200 to \$150 a lens beginning in 1994 (and that saves Medicare a cool \$50 million+).

◆ Good news—Congress restores reimbursement for EKG interpretation. Bad news—U.S. Circuit Court of Appeals allows HCFA's demo cataract-bundling project to violate

Medicare rules and proceed with a negotiated contract.

When you do not know what you are doing, do it neatly.

According to Phil Lee, MD, HHS assistant secretary for health, the nation has too many physicians. He further adds that the problem is not just maldistribution with too many specialists, but that too many physicians means costs cannot be brought under control. He believes that the changing marketplace will help, but that government intervention will be necessary. One wonders about the costs if (when) nurses are allowed to be independent providers. A serious question—Why should the government fail to do something about our real problem—too many lawyers?

Canada has never been a melting pot—more like a tossed salad.

While some politicians, many media pundits, and social planners laud the Canadian medical health scheme, Canadians are losing their sense of security about health care. All of Canada faces a lag in accessibility, particularly in highly sophisticated care. In Vancouver, patients have had to wait, on average, five weeks just to see a specialist, and another 177,000 waited up to 14 weeks for surgical procedures. Costs have escalated to \$8,600 a year for a family of four, which has added substantially to Canada's staggering national debt. (On a per-capita basis, Canada's total deficit is nearly double the U.S.) The budget problems have caused cutbacks in capital expenditures, thus further depleting funds for medical equipment. In Toronto, thousands of patients are on waiting lists for hospital admission, but 3,000 beds had to be removed from service because of staff cutbacks due to lack of funds. In an outlandish contradiction, dogs at York Central Hospital in Toronto were able to get CAT scans immediately, while humans were put on a waiting list! (*Fraser Forum*-April 93) Why? Because dog owners were permitted to pay for the scan, providing income for the hospital, while non-paying patients were restricted to a few hours each day due to the cost of running the equipment. Additional insult

to Canadians is that many of the Dominion's most prominent academic physicians have voted with their feet and moved to the U.S. in frustration. Anyone for a bureaucratic single payer system?

No matter what goes wrong, there is always someone who knew it would.

Murphy's law prevails—A one-eyed elderly woman had her remaining eye patched following glaucoma surgery. The surgeon wanted the patient to remain in the hospital for 24 hours to minimize the chance of early complications. However, he made no note in the record nor did he post any information that the patient was blind in the uncovered eye. The patient needed to go to the bathroom, but could not find the call button, which had fallen behind her bed. Additionally, her room was at the farthest point from the nursing station. After waiting 45 minutes without any attention, she attempted to go to the bathroom where she struck her head against a shower wall. She had bleeding in the operated eye, and two subsequent surgeries failed to preserve any vision. The complaint was settled for a six-figure sum.

If it says "One size fits all," it doesn't fit anyone.

"If managed competition-type organizations are the answer, why aren't more members of Congress, the President and his cabinet in them?" Rep. Pete Stark posed this query, and then introduced a bill to force members of Congress to enroll in the cheapest health plans established by the administration. This is no joke, Pete, right? And is it coincidence that the jump in tax rate, included in the Clinton budget enacted by a single vote, is just above Congressional salaries

Addenda

▲ Patients who have had pediatric cataract surgery should be followed as glaucoma suspects for the rest of their lives.

▲ Live within your income, even if you have to borrow to do so.

Aloha and keep the faith

rts

SUGARCANE WORKERS: MORBIDITY AND MORALITY

(Continued from page 303)

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ENDARTERECTOMY AND SHUNT: ALTERNATIVES OR IN TANDEM?

(Continued from page 304)

We sent the final copy for peer review to a local vascular surgeon. Here is the reviewer's comment:

"It is quite interesting to see what has been done in their [Siberian] large, centralized institutions; this collection of 567 patients with peripheral arterial occlusive disease is a very good example.

"From a scientific standpoint, the paper would not stand up to major scrutiny for peer review from one of our major vascular journals. However, when the source of the paper is placed in perspective, the statistics do become of considerable interest. One would have to question whether the series of endarterectomies versus the shunt procedures were randomized in some fashion, or whether a selection process took place. The follow-up of 2 to 5 years really represents early results in the majority of patients. The technique of endarterectomy utilizing the Vollmar rings is one that is practiced in Europe but is not practiced very often in the United States to my knowledge.

"The bottom line of rather similar results between the 2 techniques has been reported in our literature. Some of the numbers might be a bit different, but all in all the net results seem similar between the experience reported here (in the article

above) and much of the reported experience from America.

"...I think it would be interesting to many readers of the *Hawaii Medical Journal*. I don't think a great deal of editing would be appropriate or necessary to justify publication. Actually, it probably would be impossible to get reliable data."

We add one additional comment: The principal author, Igor Andrievskikh, together with the Chelyabinsk Hospital's chief radiologist Vyacheslav Sharov, were in Hawaii in March 1993. They spoke to several groups about Chelyabinsk's major problem with the release of radionuclides from the Mayak nuclear weapons manufacturing complex in the southern Ural mountains (Chelyabinsk-70). Probably of greater interest to their listeners were the accounts of life and the practice of medicine in Russia. Igor was fortunate enough to witness a balloon coronary angioplasty performed at Queen's. He was shocked after seeing the \$650 catheter being discarded. "We would have cleaned it and sterilized it for repeated use," he expostulated; "such a rare and expensive thing, in our country."

J I Frederick Reppun MD

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol*. 1991;14:146-151.

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS: Skeletal Muscle.

Antipyrexia: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a \geq 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagenicity tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/– mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0*	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecostasia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

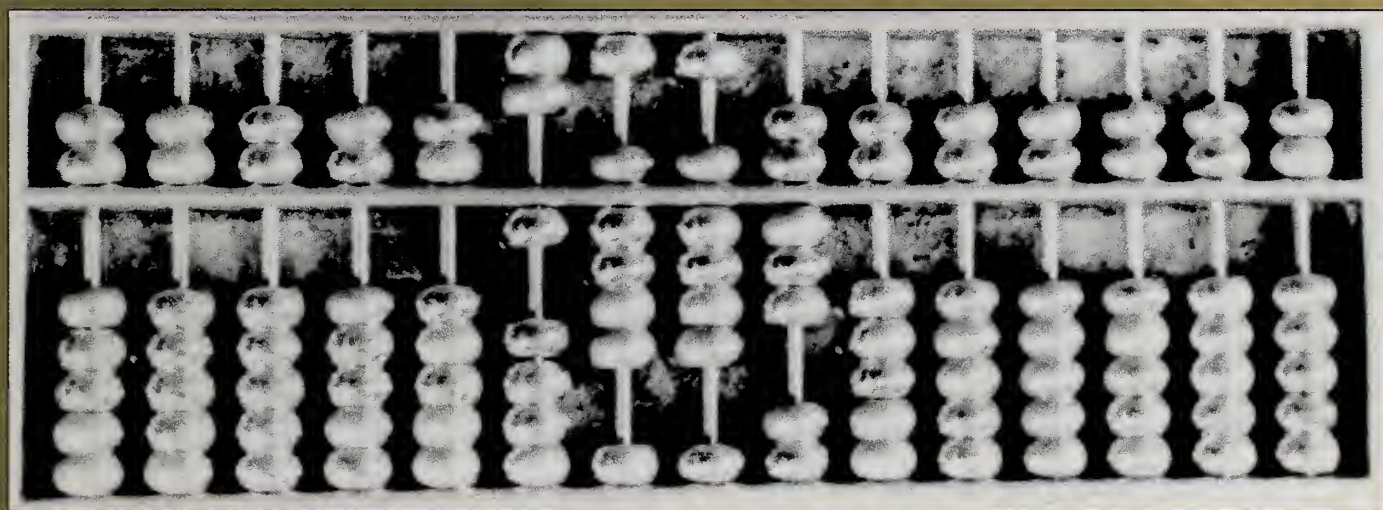


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About the Cover

The "computer" on the cover originated in ancient Babylon, rather than in China as is commonly believed. Used in the Middle Ages in the European and Arab worlds, the abacus reached Japan in the 16th century, and survives there, as well as in the Middle East, Russia and China.

This forerunner to the modern calculator and computer is still very popular today. "Chinese government officials, bankers, financiers, office clerks, junk dealers and housewives depend on their *Hsian-Pan* or "computer trays."

From bustling Hong Kong to Chinatown in New

York City, San Francisco or right here in Honolulu, fingers still are flying over the beads of abaci.

There are more than 100 different models of the Chinese abacus—in various sizes and materials. The brass and jade model on our cover is the classic model. Each of the 2 brass beads in the upper section represents 5 units; each of the 5 beads in the lower section represents one unit. Our special computer issue cover abacus indicates 1993.

Norman Goldstein MD

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A Termination

With this December 1993 issue of the *Hawaii Medical Journal*, I end my 9-year editorship with regret.

Starting with the January 1994 issue, Norman Goldstein MD will take over as editor. Norm was named the A.H. Robins Physician of the Year Award by HMA. I have offered him my assistance during the transition, and I wish him godspeed in his future endeavors with it.

I took over in the beginning of 1985 from Doris Jasinski MD, who was the interim managing editor for a few years after Harry L. Arnold Jr. MD retired; he is the founding editor and served as editor for 40 years.

I cannot quite remember when it was, but Harry used to accept my occasional editorials—from the early 1950s on, I think.

It so happens that as of the first of January 1994, Steve Lent and Crossroads Press also will have terminated their more than 18 years of publishing the *Journal*, selling ads to help fund the project and printing the issues. The charges to the HMA for doing so have not risen with inflation, the downturn in the ad market of late has made it impossible for him to continue the association with HMA without raising the rates, and the HMA is in no position to be able to absorb the increase in cost for publishing.

Consequently, the HMA Council has decided to continue the

Journal in-house. It will be printed by Pacific Printers, a company with a good reputation that gave the lowest bid to the HMA for one year.

As editor the past 9 years, I have tried to have the *Journal* be a mix of scientific articles authored by local people about Hawaii cases of interest to Hawaii readers; of medico-socioeconomic subjects focused on Hawaii. I considered it to be a privilege and a mandate to continue Henry Yokoyama's "News & Notes" that have graced the pages of the *Journal* for 25 years. Letters-to-the-editor, opinion pieces and editorials by others have been welcome, as have steady columns by Russ Stodd and Francis Fukunaga. I have taken the backlog of submissions and manuscripts as an indication that prospective authors consider the *Journal* to be worthy of their efforts. We have tried humbly to emulate the prestigious *JAMA* and the *NEJM*, but have realized that we are *small potatoes* when it comes to a comparison with those giants, who are the windows for our profession.

Perhaps we can claim to be the *sweet potatoes* relished by those of us privileged to serve as healers to our multiracial but basically Hawaiian peoples.

Aloha

J. I. Frederick Reppun MD

Computers in Medicine

The cover of a recent issue of *Fortune* magazine depicts Intel's Pentium processor chip capable of carrying out 100 million instructions a second! This is as fast as a modern mainframe computer. The June 1993 issue of *Fortune* contains a review of the changes shaking "the world's most important industry" (not health, but computers!).

The cover on this special issue of the *Journal* depicts the forerunner to modern calculators and computers—the abacus. While still used by millions worldwide, the abacus not only is much too slow, it has no record-keeping or printing potential.

There are many physicians not using computers in their practices, but they are using abaci, figuratively speaking. Physicians and other businesses and professionals in Hawaii no longer have to rely on computer authorities on the Mainland—we have them here and now!

This special issue of the *Journal* contains a vast amount of useful, practical and understandable information for our readers—even the ones who still might be using the abacus—readers not fluent in *computerese*. But, just like learning a foreign language or a new medical technology, it does require time, effort and patience—but it is so well worth it.

Randolph Wong MD, a plastic surgeon at Straub Clinic and Hospital and chair of the HMA Computer Committee, reviews a survey of members done in the spring of 1992. The number of replies was small and, because of the increased use of computers now, we will repeat this survey. Wong also includes a list of current Hawaii computer vendors.

Before her practice on Molokai, **Rachel Tortolini MD** received degrees in electronics and computer engineering, in medicine and an advanced degree in philosophy. This well-written paper is a must-read for every physician.

A joint effort by **Daniel Davis MD**, Director of Medical Education, **Gail Tiwanak RN**, Project Manager and **Lani Rauscher**, IBM System Engineer, both at The Queen's Medical Center, produced a long and very informative manuscript.

Joseph Humphry MD and **Virna S.K. Cheung MBA** have co-authored an article describing WCCHC's computerized clinical

information. Dr Humphrey is an internist at WCCHC and associate medical director at HMSA. Virna Cheung has more than 10 years experience in systems analysis and programming. She is the system manager at WCCHC.

Psychiatrist **Harry Chingon MD** has a BS in computer science and a medical degree from the University of Hawaii. Now a third-year resident, he describes a rather unique psychiatric program used at The Queen's Medical Center emergency room—another interesting use of computers.

Another psychiatrist **Enrico Camara MD** came to Hawaii in 1992 after completing his residency at the Cleveland Clinic. Camara describes some very exciting visual and auditory adaptations of computers in his "Virtual Reality" paper. "We must be more comfortable with Virtual Reality...lest we miss the chance of becoming virtual doctors," he writes.

Calvin Delaplain MD began as an engineer, attended West Point, studied at Letterman, then came to Tripler Army Medical Center where he is a Lieutenant Colonel and chief of the nuclear medicine service. Collaborating on these 2 papers dealing with Telemedicine were **C. Eric Lindborg MD** at Kwajalein Atoll and chief of dermatology **Scott Norton MD**. Norton also has a master's in public health and tropical medicine with special interest in ethnobotany. Tripler Army Medical Center Commanding General **James E Hasting MD**, Brigadier General, Medical Corps, has been very supportive of the telemedicine projects. We look forward to an expanded network with telecommunication ties throughout the Pacific, both with civilian and military medical facilities.

Jerry Fuqua PhD, who has a background in physics and physical oceanography and in several different computer operating systems, and **Robert Peterson MD**, plastic surgeon at the Kapiolani Medical Center for Women and Children, present an excellent review of their experiences and make some practical recommendations to the neophyte.

Following this paper is one by another plastic surgery team.

(Continued on page 354) ►

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Thoughts on Finding the Right Computer Buddy: A Moveable Feast

Rachel Tortolini MD, BSCS, BSEE*

The burgeoning supernova of medical information is rapidly overtaking the practicing physician's envelope of comprehension. More physicians by necessity are turning to automated resources as a means of amplifying the information they need to know while, at the same time, reducing the volume of technical pollution. Computers are capable of being a silent partner at your side as you talk with your patient—ready to cut to the quick and retrieve the latest information for the particular clinical problem at hand.

Computers can be considered an extension of the brain. In a sense, they are silicon-based "life" forms. Virtuosity is learned from them as familiarity is gained—the same as becoming acquainted with a human stranger. This article is about one physician's solution to the problem of too much information. It's unabashedly anecdotal but we hope the reader will glean some hints while navigating through the realms of cyberspace.

A Brief Trip into Cyberspace

Many physicians are unfamiliar with computer technology. As in medicine, computer technology has its own jargon. Anatomy cannot be discussed clearly without the vast superstructure of Latin and Greek jargon tagging along. This is reasonable, since new words are needed for new objects.

Computerese, like the computer itself, is very much with us. To become computer-literate, the jargon needs to be mastered as well because everybody who is computer-literate uses this jargon everyday. The English language is a fungating mass of verbal accretions that once were jargon a century ago and now are part of the common tongue.

Physicians need to learn computerese because they need to converse with persons in computer sales and service; physicians need to buy software and hardware intelligently, and they need to avoid being taken advantage of by hucksters who can spot a computer rube. The glossary in Appendix B is a representative sample of jargon commonly encountered and used in this article.

Explaining how a computer works is difficult but physicians must have a good sense of the beast by using a few good metaphors. The computer can be understood in terms of its structure and function: Its structure is similar to that of a post office and its function similar to a symphony orchestra. If you think the latter comparison seems far-fetched, just lean an FM radio against the computer while running a program and listen to the music of cyberspace.

Structure

Imagine the Honolulu post office for a moment with its hundreds of thousands of post-office boxes. Each box has an address and contains information in the form of mail placed in it every day. Behind the boxes are the postal workers.

They pick up incoming information and put it in the boxes, whether locally or farther away. Some people come to the post office, take the letters out of their boxes, and use the information. Other people write letters containing useful information and send

them through the mail boxes elsewhere. The postmaster tells all the postalworkers how to run the post office according to a personnel manual written by bureaucrats in Washington and stored somewhere in the post office.

The computer is like the post office. The form and content of the postal boxes represent the addresses and data in this metaphor. These are expressed as binary numbers in a chain as long as 32 bits—equivalent to billions of addresses (2 to the 32nd power).

The mail that goes into the boxes is the data stored in the computer the capacity of which is specified by 16- or 32-bit numbers which code for instructions, numbers, letters, or any other kind of information. Each data and each address bit is carried electronically by a single wire or "trace" on a printed circuit board of the computer, called the mother board. Thus, a 32-bit address, or datum requires 32 parallel wires each. Each group of 32 wires represents a bus.

Contemporary personal computers (PCs) have 32-bit address and 32-bit data buses on their mother boards. Both buses originate in the computer's central processor or microprocessor; this electronic chip is equivalent to our postal workers. The processor sends and receives data to and from other devices on the data bus selected by an address on the address bus; this sort of talking back and forth is called handshaking.

All computer devices except the central processor have an address on the address bus and all devices hang onto the data bus in parallel like fresh laundry on 2 clothes lines. Devices do not conflict with each other because each device's address is exclusively its own and answers its calls.

Now, the postmaster is the program that runs the postal workers in the microprocessor—called the processor's "micro-code"—that resides on the chip. The personnel manual is software called the basic input/output system or BIOS that is located in another chip in read-only memory or ROM—a device that also hangs out with the other devices on the bus.

Our post-office workers are quite nosy; they open all the mail and process the contents before they send it to the next destination. Some of the mail's contents (data) even tell the postal worker where to send the mail next; these pointers are responsible for the power of the computer—its ability to represent addresses as data which can be processed and turned back into addresses again. Advanced addressing instructions in the Motorola 68000 chip made the Macintosh a superior computer.

Sometimes the postal workers are too slow at handling double precision numbers—ones that require twice as many numbers to the right of the decimal point. Therefore, an assistant called a math co-processor, similar to an assistant postmaster, is called in to speed up the mail.

Micro-code is beyond the scope of this paper but it is essential to know that the BIOS chip is crucial to operating the computer. BIOS firmware tells the microprocessor how to get access to the devices on the bus—from disk storage, to ports, to displays. It interprets the instructions from the operating system—the personality of the computer—in terms of hardware. The BIOS version needs to be kept up-to-date in order to run the latest operating system.

Most devices need more than one postal box to work; in fact,

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if one postal box represents one bit of information, then the video display, for example, needs as many postal boxes as there are dots or pixels on the screen—more than a million for today's high resolution color displays. Each pixel has an address to which the processor has access according to the BIOS instructions. In the graphics mode, a processor analyses each individual pixel so that very sophisticated color presentations can be made. Sometimes the postmaster needs an assistant because the pixel calculations can't be handled fast enough and a video co-processor is given the task. In text mode, BIOS uses a look-up table to tell it how to display a character for the display; this is generally a limited way to display data.

External devices, such as printers, need data spigots called ports; these spigots need as many as 16 addresses in order to operate. BIOS requires thousands of addresses in a large block of memory in order to function. Random-access memory, or RAM, also needs as many addresses as there are bits of data. Disk devices need addresses as large as input and output ports—these are called channels. Remember that all postal boxes are capable of carrying 32 bits of information in billions and billions of combinations because all devices are connected in parallel to the same data bus. A 32-bit address bus allows the computer to access billions and billions of postal box addresses. Remember the address bus is separate from the data bus and each device is attached in parallel to each other.

Function

We have described the computer's structure in space but not in time. To explain the computer's function, imagine a symphony orchestra. The orchestra consists of the various devices on the address and data buses. Each musician has a place or address in the orchestra and each musician has a score or data in front of him or her. The conductor is the central processor. The score is the program to be run—primarily the operating system within which other programs run as sub-routines.

The instructions for how to interpret the score are in the mind of each musician. The conductor has a micro-code and the musicians have their BIOS and firmware to tell them how to interpret the score into the music that comes out of their instruments or devices.

In the background a metronome ticks setting the rhythm of the score. This is the computer's clock. With every tick, an instruction is loaded into memory, instructions and addresses are decoded, data is processed, data is stored in devices, and new instructions are fetched from other devices. The notes of the musical score are read, interpreted and played. Music is made.

Computer clocks run at millions of cycles a second or megahertz (MHz). On modern computers, each command takes less than a millionth of a second to execute and hence computer power is measured in millions of instructions a second, or MIPS. The latest microcomputers are pushing over 50 MIPS, or what a small Cray super-computer in the early 1980s could process.

In summary, the computer is a kind of post office that acts like an orchestra. In other words, a bunch of musicians who hang out together on a bus waiting for a letter from Satchmo in their postal box telling them how to play a riff.

With an apology for mixing metaphors, let us proceed to selecting a computer-buddy. Once again, please refer to the glossary for review of unfamiliar terms. By the time the reader finishes this article, he or she will be talking computerese with the best of us and turning that knowledge into informed purchasing decisions.

Selection criteria

Criterion One

Our definition of the ideal computer is one that isn't there yet. Computers should allow a seamless, transparent area of contact with the information coming in or going out. After all, we're after information, not Tinkertoys; these devices are tools, not fetishes. Computers now are portable enough to offer minimal hassle to

the user's life-style. Hence, transparency is the first criterion for selecting a computer.

Criterion Two

The kind of information to be processed should be considered. Define the kind of data to be searched for. Is it on-line services, data bases, simulation, instruction, and so on? Next, find the software to fit the desired information—pick the software to reflect the data—and then always select the hardware to fit the software, in that order.

Next, fit the software to your brain. How do you think? Are you an intuitive thinker or one who is more linear? Some people love graphic displays, while others prefer text-mode and staring at the DOS prompt. What kind of cognitive operations will you be doing with the information the software dishes out? Will you be doing much searching, sorting, listing, reporting or will you be crunching numbers, creating art work, creating ideas or objects that require massaging of the data? Generally, software that is not easy to use also is not very useful. That is why graphical interface software, like Microsoft's Windows is preferred.

Criterion Three

An intuitive thinker would find it important to get a computer good at "disk-intensive operations." A computer with a fast seek-time is appropriate for locating information quickly on a storage medium; a fast hard-disk, for example, would be something needed in a computer more than a fast processor.

On the other hand, working with ideas or pictures requires much number crunching. In that case, a computer that is good at "processor-intensive" tasks such as the latest chip with the fastest clock and bus speed is desirable. A math co-processor will speed up spreadsheets and graphics as much as 700%. To go on-line, then, the fastest modem available is needed: Nothing slower than 9600 baud. Distinguish between "processor-intensive" and "disk-intensive" computers—the third criterion.

Criterion Four

A word of advice is offered concerning selection of hardware and software. Criterion Four is a corollary to Criterion Three: Never use a software utility to fix a hardware problem or deficiency. For example, many people are buying disk-compression software as a cheap alternative to increasing the storage capacity of their hard-disks. The failure rate for such software is much higher than competitive compression-code residing in "firmware." Disk-compression software on a magnetic disk is subject to data corruption and is not robust enough to recover from disk crashes. The result is a disk that one day simply doesn't respond and only a low-level format will recover its use. If the data isn't backed up, the consequences could be disastrous to a business.

Microsoft's MS-DOS 6.0 contains a "disk-doubler" but it is only marginally more reliable than other compression software that has been incorporated into the operating system. When suffering with "RAM-cram," either a larger physical storage medium (more RAM, more replaceable media, or more hard-disks), or a disk-compression board with its software in firmware should be considered. It is very unlikely that firmware will accidentally flip a bit, as do the software versions. In any event, always back up the data.

An exception to the above corollary might be the memory manager utility. It provides Microsoft's MS-DOS operating system with upper, expanded and extended memory. This is only an apparent exception to the rule; it is really a Band-Aid. Memory managers are the tribute the buyers of IBM equipment pay for Microsoft's Jurassic DOS operating system design.

At the time IBM designed its very first PC in the early 1980s, in its great wisdom, this computer giant thought that no personal computer would ever need more than 64 kilobytes of conventional

(Continued) ►

memory to run programs—equivalent to about 30, single-spaced, typed pages. Microsoft and others convinced IBM to increase this limit to 640 kilobytes, which is the present DOS standard. As current sumo-sized programs now weigh in at several megabytes each, this memory limit has become a straitjacket.

Software engineers have reclaimed unused upper memory with various memory management tricks such as paging (Lotus-Intel-Microsoft—LIM 5.0 specification-expanded memory) and an extended-memory bus addressing Microsoft's XMS standard specification. Microsoft is trying with Windows NT and Windows/32 to simply rewrite DOS the way Apple did it 10 years ago.

At that time, Apple had design control over the entire architecture of its Macintosh computers from the beginning. They chose the Motorola 68000 series microprocessor—with more powerful addressing instructions than Intel. IBM has always used Intel's 80n86 (where $n=2,3,4,5,\dots$) series microprocessors. Apple's programmers wrote an intuitive operating system for the Mac employing essentially open memory mapping for running programs. Fortunately for Apple customers, of course, Macintosh has never had RAM-cram; its "open" memory map was designed to be limited only by the physical memory available—not by the software.

IBM Microsoft's mistake in design was paid for by all of its customers. They essentially subsidized the industry's re-engineering of the PC to the point where today's IBM looks like a Mac, talks like a Mac, walks like a Mac. Along the way, IBM has been drawing customers away from Apple with the promise of super microprocessor chips and "WYSIYG" (What you see is what you get) interfaces. Apple sales are taking a downturn as a consequence.

Criterion Five

The converse to the above criterion is not necessarily true, however. Hardware frequently can fix a software deficiency or problem. Criterion Five states: Whenever possible, put as much software onto the hardware as possible. An example is slow video-graphics speed. Software publishers still peddle utilities to speed up, compress and generally bolix the video-display devices. Many manufacturers are moving to local buses for video-processing chores. Local buses are akin to distributed or parallel processing. A co-processor, similar to a math co-processor together with its own RAM on the video board, does all the computations required to produce a graphics image on the screen. This little computer in itself is faster because the local bus can run at data-speeds far greater than the speed of the main processor's data bus.

Criterion Six

In general, virtual processor speed can be traded off for virtual memory. The word "virtual" is used here to describe the number of resources apparently available to the user. The total amount of resources is the user resources plus the internal resources required for the computer's housekeeping. For example, disk-compression recognizes redundant information and eliminates it. After compression, the disk looks larger than it really is; the "fat" has simply been eliminated. To accomplish this trick, the processor spends extra amounts of time coding and decoding files every time the disk is accessed. This slows down the processor-intensive tasks available to the user. Hence, virtual memory goes up as virtual speed goes down. The same applies to speeding up disk-intensive tasks. Here a disk-cache, RAM disk, or extended/expanded memory-enhancement provides access to data at electronic speeds. The principle behind this is that the next disk access will most likely be near the last access on the disk. Hence the computer will load an entire block of the disk into electronic memory in order to by-pass the very much longer seek-time of the disk. Processor speed is improved

a thousandfold but at the cost of more electronic memory being taken from running programs. In other words, as the virtual processor speed goes up the virtual memory decreases. Therefore, for any given system with a fixed amount of resources, the product of available user-memory and available user-processing speed is a constant. In other words, Criterion Six states: Disk-intensive and processor-intensive tasks are mutually exclusive and must be traded off one against the other.

Criterion Seven

Of course, technology marches on and the performance values used here certainly will be obsolete by the time this goes to press. The seventh criterion is, therefore: The most advanced computer needed is the one that will do the job given the information that is needed. The computer wanted is the computer that will be used. This also applies to software; the most useful software is the one that is easily used.

An old IBM personal computer is still very useful for peripheral tasks like an office telecommunications system or as a laboratory instrument-control processor. We recycled our 2 used IBM-XT clone-computers to store recipes and diet information in the kitchen and to run our voice-mail system in the office. Both jobs required only good disk-intensive ability. Unless the user plans to design nuclear weapons in his or her spare time, the new Alpha, RISC, or Pentium super-microprocessor chips are pure overkill for the average physician in private practice. A group practice with a local area network might consider the advantages of a 32-bit operating system such as Windows NT, but processor-intensive tasks should be located in the workstations that hand-shake with the LAN file-server's disk-intensive operations.

Criterion Eight

Never get locked into a system that uses exclusive vendors for hardware or software. Even though a new whiz-bang computer is technically superior, if it is not on the open market, widely used and supported by thousands of vendors, the consumer will be paying many times what the technology is worth.

Consumers should buy software and hardware that the majority of customers are buying, even though they may have features that are inferior to the dream model. Mass marketing causes other software designers to incorporate the most-used software "hooks" into their product at affordable prices.

For example, there are many other manufacturers of multimedia soundboards, but Creative Labs' SoundBlaster sold the most products and its code became an industry standard.

In software, MS-DOS was a pretty poor operating system, but the prestige of IBM made it a standard. The other operating systems designed for the Intel chips are now pushing up daisies. Macs were a vastly superior machine to IBM but again prestige pushed the IBM PC into a majority market position. It became the standard.

When manufacturers market a new product, they design it for mass appeal. This pressure to conform is not innovative, but it is the way the market works. Criterion Eight: Stick with the tried and true—even though the product is not so hot, it's supported. A corollary to this Criterion is to pay a little bit more for a product that is backed up by customer support service.

Criterion Nine

The Ninth Criterion concerns the question about what "platform" to select. A platform is the operating-system environment that the computer uses to handle housekeeping and coordination of the hundreds of devices used for input and output. Here the

(Continued on page 320) ►

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*Steve Clason, M.D.
Ophthalmology*

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(Continued from page 318)

software and the hardware together determine the computer's personality. Pick a platform that satisfies all previous eight criteria.

Are you a Mac person? Do you like Pen computing? Do you like the IBM man's suit? Is NeXT in your future? This all depends on how much you are willing to pay for a computer-buddy.

Open memory-mapping with open hardware architecture is recommended. Open memory means the user uses all of the computer's physical memory to run programs—unlike the early PCs but like the Macintosh.

Open hardware means the user can have expansion capability (slots and sockets) to use second-source vendors to upgrade or customize the system economically—unlike early Macintosh systems but like the early IBM PCs.

Also recommended are true 32-bit data and addressing in the operating system such as OS/2 and Windows/32. This simply means the user is using the current chips at the capacity they were designed to handle.

NeXT is a very expensive and impressive Unix-like workstation whose cost-effectiveness for the physician makes no sense. Macintosh is a friendly, easy-to-use computer but it costs twice as much as a comparable IBM-clone product and is generally slower. Nowadays, with the new graphical displays available, such as Windows, OS/2 Version 2.1, Norton Desktop, or Hewlett-Packard's New Wave, there is very little difference except the price between the Macintosh/Quadra and the IBM clones. Market pressure is forcing Apple to discount its line steeply.

IBM has a higher profile in the business and nerd worlds. Intel microprocessors currently are the fastest, so IBM computers generally are faster than Macs. Macs attract graphic artists, educators, and other people who are more concerned about Criterion One. In the future, the distinctions in hardware will continue to blur across platforms until all platforms eventually will be interchangeable. IBM and Macintosh platforms already are able to run each others' operating systems. Computers are essentially a commodity.

A System to Consider

Given these 9 criteria, here is a system that we like a lot. We chose the IBM ThinkPad 700C (and the later models 720C and 750C) mainly because it is half as expensive as a comparable Apple computer; a comparable color Macintosh Notebook doesn't exist at the time of this writing). It has the largest color VGA screen (10.5 inches) in its class (Do not pooh-poooh a color display; modern software uses color to convey information rather than just to look pretty—it is an added dimension of information.)

The ThinkPad uses a 486SLC processor at 25 Mhz. The SLC series is a low-power consumption Intel 486SX made for notebooks. The 25 Mhz chip is upgradable to a clock-doubling 486SLC at 50 Mhz. With an additional 38SLC co-processor chip, the numbers will crunch, crunch, crunch.

Generally our tasks are disk- and modem-intensive, so we don't need the processor speed. The ThinkPad has a fast, removable, 120-megabyte hard-disk that allows the user to upgrade to a larger capacity, or interchange disks between offices or for security reasons. We like the computer's notebook portability; it will run on a rechargeable battery

for about 2 hours on a long plane flight.

Our entire system works on rechargeable batteries and there is even a manufacturer of solar panels made to run the entire system if the user is out in the Australian bush doing medical relief work.

The ThinkPad was a "best buy" in a recent survey of notebook computers in *PC Magazine*.

We're more intuitive and graphically oriented so we run Norton Desktop with Windows 3.1—not ideal, but it will do until Windows/32 comes out. We have access to medical data bases using a battery-operable NEC Intersect CD-ROM reader that feeds into the ThinkPad's parallel port through a SCSI adapter that doubles as a printer port attached to the back of the printer. We chose the battery-operable Kodak/Diconix 701 ink-jet printer, a best buy according to *PC Magazine*. It gives us laser quality WYSIWYG printing without the laser.

The software for our compact disc (CD-ROM) includes the *PDR Merck Manual*, *Family Practice Medicine*, *Family Physician Magazine*, *STAT!-Ref*, Little Brown's *Maximum Access to Diagnosis and Therapy (MaXX)*, *Scientific American Medicine*, *Clinical Dermatology Illustrated* and the *Family Doctor*. We use them daily in our office practice. The latter CD, along with *Bodyworks*, are excellent patient-education programs. Recently an even better program called *A.D.A.M.* became available; it dissects the human body. We run drug-interaction reports using Medical Letter's *Drug Interaction Program* and a special facility inside the *PDR* program. As an adjunct to CME, we run Scientific American's *DiscoTest* patient-simulator program for credit. *Clinical Dermatology Illustrated* comes with a 20-CEU test. If we have a tough internal medicine problem, we run the

patient data through the *Iliad* Expert System for ideas. The program also doubles as a patient-simulator. Anything we can put on the screen can be printed out for patients to take home.

We are always looking for good practice-management software, but alas, we have not found a single one that we like. Most



Figure 2: Note the connector on back of printer is parallel to SCSI ("scuzzy") adapter. Black boxes on counter are power cubes for line operation.

are MS-DOS text-mode programs limited to conventional memory-usage and interfacing. Many still require an experienced encoder which is the lion's share of the work of billing. Also, few practice management programs seamlessly integrate all office functions including clinical records.

Doctors need to get together with programmers experienced in object-oriented C++ programming in order to design a transparently cost-effective Windows program for clinical notes, and for billing and coding that takes advantage of the new operating system's full capabilities for multi-tasking and for multiple access. Remember, software that is not easy to use is also not useful.

We send and receive faxes using the Lotus *Ami-Pro 3.0* word-processor through a fax/modem and software. We created our own ICD-9 and CPT-code reference data bases, using *Microsoft Access*, an easy-to-use data base program. Office and personal accounts are kept on *Quicken for Windows* and update our credit-card expenses and pay our bills on-line through *CompuServe*.

Installed inside our notebook is a 14,000 baud modem. If we can't find an answer in the local system, we have regular access to *CompuServe* through the modem as a gateway to *Dialog*,

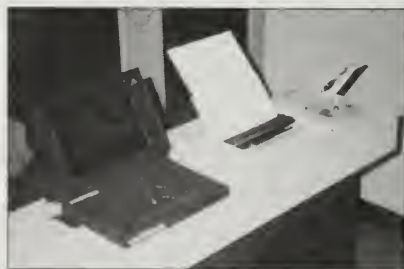


Figure 1: Complete computer office set-up. (Front view)

Knowledge Index, *BRS Coll-eague*, *Index Medicus*, and a hundred other data bases, forums and services. On-line services work as fast as our own system at 9600 baud or above, such that they meld seamlessly and transparently with our own system. We use *Prodigy* occasionally for the fun of it, but it is not an on-line service for the office. The powerful InterNet system is worth looking into but we were not impressed by its primitive user interface. However, through InterNet, computers at major private and government research institutions worldwide can be interrogated.

Our entire system, including software described above, packs into a leather Targus briefcase that fits under an airline seat (Figure 3). Since we do much *locum tenens* work, the system is a valuable sidekick that has already paid for itself.

So, we hope we have convinced the reader that computing is truly becoming a *moveable feast*. This article was composed, written and faxed to the *Journal* on the above system.



Figure 3: Entire office computer system with CD-ROM software packs into a Targus carry-on bag that fits easily under air line seats. Extra roomy for clothes or cosmetics case.

Hardware

IBM ThinkPad Series notebook computers with 10.5 inch SVGA flat color screen, 120 MB or 240 MB removable HD, 14400 FAX/modem and nickel hydride battery. Two-year warranty on parts and labor supported by 24 hour 800-line.

NEC Intersect CD-ROM Reader with NiCad battery and SCSI to parallel converter and printer port.

Kodak 701 Diconix Printer with NiCad battery.

Targus leather computer briefcase.

Software on CD-ROM

Scientific American Medicine and **DiscoTest**

Medline, Family Practice Subset, Macmillan Multimedia

MaXX, Maximum Access to Diagnosis and Therapy, Little Brown Publishers.

Family Physician, Creative Multimedia.

STAT!-Ref, Teton Data Systems.

Family Doctor, CMC Research.

PDR On CD-ROM including Merck Manual.

Clinical Dermatology Illustrated, CMEA.

Software on Floppy Disk

Iliad, Internal Medicine Expert System, AI Systems.

Bodyworks, Software Marketing.

Medical Letter's **Drug Interaction Program**.

Sources

CME Associates, CD-ROM Software, 1-800-227-CMEA, 4015 Hancock Street, Suite 120, San Diego, CA 92110.

Penguin Portables, Notebook Computers and Accessories, 1-800-241-1096, 119 Witmer Road, Horsham, PA 19044.

The Medical Letter, 1000 Main Street, New Rochelle, New York 10801-7537.

Computer Discount Warehouse, 1-800-578-4CDW, 2840 Maria Avenue, Northbrook IL 60062.

Micro Warehouse, 1-800-367-7080, 1720 Oak Street, POB 3014,

Lakewood, NJ 08701-3014.

Applied Informatics, makers of *Iliad*, 1-800-584-3060, 295 Chipeta Way, Salt Lake City, Utah 84108

Keyword Publishers, distributors of A.D.A.M., 1-800-945-4551, 482 Norristown Road, Suite 111, Blue Bell, PA 19422.

Magazines

PC Magazine, **PC World**, **Mac User**, **Mac World**, **Computer Shopper**, **Windows User**.

On-line services

CompuServe, oldest on-line service with fairly good interface and good medical information, 1-800-848-8990.

America On-Line, CompuServe look-alike with excellent user interface but very little medically oriented information, 1-800-87-6364.

Delphi, InterNet Gateway, 1-800-695-4005, clumsy interface but best access to medical information.

Prodigy, a frivolous service for home use. Hundreds of bulletin board services (BBS) exist for medical information and are too numerous to mention here. Check the file finder on CompuServe for files containing lists of BBS.

Appendix B

Glossary

Artificial intelligence. Software emulation of the human thought process—a virtual mind—with broad ability to make inferences in random contexts and situations.

ASCII. A table of 25 hexadecimal codes for numbers, letters, graphics symbols, control codes, and foreign language characters established by the American Society of Computer Manufacturers. Text mode computers use ASCII codes in tables to tell their displays how to create a character on the screen without having to calculate each pixel. Use in less powerful computer systems.

Back-up. Copying information in a hard-disk onto a more reliable storage medium. One must have a regimen to back up important data to protect against the inevitable disk crash.

Baud rate. The number of characters per second that are sent over an asynchronous communication system like telephone modems. Each baud consists of an ASCII character code plus extra bits responsible for handshaking and error correction. The baud rate is generally slower than an equivalent synchronous data transmission due to the added bit overhead.

Boot. The act of giving the boot, from bootstrapping or lifting oneself up by one's bootstraps. Booting starts up the computer either by resetting the system clock (cold boot) or from software (warm boot). Either way, booting provides pointers to addresses in BIOS of start up routines.

Boot sector. An area on the storage disk used by the operating system to start the computer from disk. It contains the addresses for BIOS commands as well as tables.

Byte. A 4-bit binary number. A byte can code as many as 2 to the 4th or 16 possible states. Two bytes code for the ASCII set of 256 characters. A double precision 4-byte code could allow for 35,536 characters.

Clock. The master chronometer of the computer which synchronizes all activity on the buses (see synchronous communication).

Controller. A smaller scale processor with an even more restricted capability than a co-processor. This chip controls the channels to the disk storage units. Controllers take a request from the bus and translate it into an exact disk function necessary to find the data, read or write it on disk, and put the data on the bus.

Conventional memory. Core memory where the programs reside so that the processor always knows where to look for them.

Co-processor. A microprocessor in its own right, designed to perform a specialized housekeeping function and occupies a device address on the bus.

Cyberspace. A lyrical description of the virtual world inside computers. Coined by William Gibson in the novel *Neuromancer*.

(Continued) ►

Data base. An accumulation of data organized in a special way that allows easy access and manipulation. The data base program takes records in files and generates forms, reports and tables based on inquiries.

Data Compression. A technique of compacting data into a smaller memory space by taking advantage of the redundancy inherent in certain kinds of data. For example, English text is over determined by unnecessary characters such as spaces which do not add any extra meaning to the text. Algorithms exist that reduce the text without changing the data. For example if the spaces were removed from between words; the reader wouldbestillabletoreadthissentence.

Disk cache. A method of speeding up disk access by creating a block of RAM—a cache—where large amounts of data from disk can be squirreled away. The next disk access is usually from the same area of the disk that the last disk access was drawn. Therefore, the data around the last disk access is loaded into cache and accessed from RAM at electronic speed. A disk cache speeds up the effective seek-time for disk access by a factor of several hundreds. A large cache can service up to 80% of disk requests and approaches 100% as the cache size approaches the disk's size.

Disk crash. A corruption of data on the hard disk such that the disk cannot be accessed or will not work correctly. Usually disk crashes originate by flipping a bit in the file allocation table or boot sector of the disk. Crashes are caused by viruses, failures in the media or just plain quantum uncertainty.

Disk-intensive. An operating system task that occupies the majority of the central processor's time in servicing accesses to mass storage. Data bases are paradigmatic.

DOS. Disk Operating System refers to any operating system that stores its programs on a disk storage medium. The most advanced operating systems are System 7, OS2, and Windows NT which are true 32-bit addressing programs utilizing the full capability of current microprocessors. MS-DOS is simply Microsoft's version.

E-Mail. Electronic Mail. Mail between workstations on a LAN or over an on-line service.

Expert system. An evolution of artificial intelligence consisting of a data base of IF...THEN inferences garnered from experts in a specialized field of learning such as internal medicine and a program (inference engine) which interprets inquiries by sorting through the inferences based on likelihoods.

Expanded memory. A technique of addressing memory that increases the memory available to the system. A block of unused upper memory is set aside as a window called a "page" into an expanded memory device. The computer relies on the device's controller and a special software utility to access this memory. The memory cannot be accessed unless programs have this special software (LIM Version 4.0).

Extended memory. Memory available to the computer beyond the addressing capability of the processor, bus or operating system. Special software in the operating system is used to extend addressing. The computer accesses this memory as if it were really an extension of the address bus. Sometimes called virtual memory (Microsoft's XMS specification).

FAT-File allocation table. An area on the storage disk that keeps track of where to find the files stored on the disk. If the FAT is corrupted, there is no way to find the files and they are lost. Some software utilities save a copy of the FAT so that the disk can recover from a crash.

File Server. A LAN computer not assigned as a workstation. The file server is similar to a librarian who gets the book wanted. A LAN computer which contains the majority of the mass storage of programs and data in the net and runs the network in some LANs. Workstations get their files and programs from this computer.

Firmware. Software coded into computer ROM chips so that they are indestructible. Firmware is immune to viruses and other causes of disk crash.

Format. Either a verb or noun. To format a disk means to divide

the disk up into electronic sectors and create a FAT and boot sector on the disk. After this is done, the disk is called a formatted disk. The disk is bootable or not depending on whether the operating system is copied onto the disk in the boot sector. In this way the disk controller and operating system have pointers to any files given to the disk or read from the disk. It also can contain enough of the operating system to boot the computer.

Gateway. An on-line service providing access to other on-line services and networks. Some on-line services contain gateways themselves; example, InterNet, a world telecommunications network between computers in the major research and governmental institutions of the world including the old Soviet Union.

Handshake. The protocol required in order for 2 devices to talk or exchange data with one another. Modems handshake other modems; printers handshake with computers; computers handshake with other computers—hey, it's a beautiful world!

Hexadecimal. A number based on 16 rather than the binary base-2. If 16 is the 4th power of 2 then any hexadecimal number is equivalent to a 4-bit binary number. It is a way of writing large binary numbers in shorthand. For example, instead of writing 2 (base-10), we can write 0010 in binary or 02 in base-16. Ten in base-10 is 1010 in binary and 0A in hexadecimal. Letters A through F are used as numbers 10 to 15 in hex. Most computer math is expressed as hexadecimal or hex for short. Thus the address 73,728 (base-10) is 1010,0000,0000,0000 (base-2) or C0,00 (base-16). This is the starting address for BIOS in some computers. On the memory map, C0,00 starts at the point 00 on the X-axis and C0 on the Y-axis. The Y-axis hex number is called a "page" of memory.

Computer Language. A system of writing operations in terms understandable to humans that can be translated into commands that machines can understand, or machine language. "C++" is a language commonly used in modern microcomputers.

LAN—Local Area Network. Autonomous personal computers interconnected by a communications network in order to share programs and data between them. In general it refers to all the software, hardware and firmware necessary to accomplish this task.

Local Bus. A bus which operates within a device to speed up the device's function by operating at a higher clock speed than the mother board's bus can physically tolerate. It is usually associated with some kind of co-processor—an evolution towards parallel and distributed processing.

Memory Map. A layout of where each device resides in terms of its address as a pair of 2 hexadecimal numbers. Thus, the address hex number C0,00 represents the location (00,C0) in Cartesian coordinates on the map. Memory maps help conceptualize how efficiently memory can be utilized. It also helps fix bugs in sick computers by using software utilities.

Micro-Code. Firmware programs written in binary numbers residing in the microprocessor chip tell the programmable logic circuits inside it how to do functions coded as instructions in the computer's machine-language such as addition, subtraction and addressing. Machine-language is the form in which the operating system is written. Micro-code basically decodes machine language instructions so that the microprocessor can create hardware circuit connections which will follow the machine-language instruction.

Mother Board. A printed circuit board which connects together the buses, ports, channels, RAM and ROM memory, BIOS, microprocessor chips and expansion connectors responsible for the operation of the computer.

Multi-Access. The ability of many workstations together to have access to the same computer, virtually at the same time. LAN operating systems allow the network to schedule accesses to file servers, peripheral devices and work stations according to a handshake protocol. The system looks to be simultaneous because all events happen at electronic speed.

Multi-Tasking. Advanced operating-system techniques allow

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(Continued from page 322)

many programs to operate virtually simultaneously on the same computer. The computer's memory and processor is divided into many virtual machines. Each program is assigned a virtual machine to run on, as if it were the only one running in the system. For example, OS/2 allows an Intel 80486 microcomputer to simulate as many as 15 Intel 8086 machines (the original IBM-PC), giving each a custom configuration and program. All programs appear to run simultaneously because events happen at electronic speeds.

Number-Crunching. Taking raw data, massaging it with the computer and turning it into a finished product.

Object-Oriented Programming. A method of modular programming such that all software tasks become completely self-contained programs on their own, with a set of generalized inputs and outputs. Each module runs simultaneously in a multi-tasking operating system and is considered an object represented by an icon describing its structure or function. Programming with objects becomes a matter of creating the right objects and connecting them so that they serve together a greater purpose than themselves. This concept simplifies the job of creating new programs for applications. Languages such as C++ by Bell Labs and Borland Software enforce top-down programming design and a robust, fault-tolerant, reliable code. Consequently, the software is easy to use and useful.

On-Line Service. A telephone network providing computer access by modem to useful services such as databases, e-mail, forums, free programs, shopping services, games, news, and many others. Examples: Compuserve, Prodigy, America On-Line.

Operating System. The only program a computer ever runs. Surprise! The program booted up is merely a sub-routine in the operating system. The operating system translates the wants and needs of the introduced program into commands understandable to the BIOS, controllers, and processors.

Platform. A term referring to an operating system that can run on any hardware and, therefore, is portable. Also used to describe a computer's combined hardware and operating system. Thus, Mac and IBM operating systems are platforms that can run on each others' machines and, therefore, Mac and IBM are platforms that can run each others' programs, exchange data and communicate on a network.

Processor. The device responsible for operation of the computer. It controls addresses and manipulates data on the bus.

Processor-Intensive. An operating-system task that occupies the majority of the central processor's time in computation of addresses and data. Graphics are a good example.

RAM-Random Access Memory. Electronic storage circuits capable of being accessed by the computer individually and thereby at random using direct addressing. The computer can obtain data from RAM faster than from mechanical disks because it operates at electronic speeds. Faster by more than a thousand times, RAM is used to simulate mechanical disk storage as virtual disks or RAM disks.

Robust. A term describing the ability of software or hardware to tolerate bugs, glitches, viruses and other flora or fauna that inhabit a computer without causing it to cease completely to operate, or to lose its capability to function usefully.

ROM-Read Only Memory. Electronic or optical media which are recorded only once and are forever fixed in circuits or plastic. Like a phonograph record or photograph, ROM can only be read. It is therefore safe from crashes that plague media that can be written on. Programs stored on electronic ROM chips are called firmware since they are indestructible. SCSI (Pronounced "Scuzzy") A technique for daisy chaining a series of storage devices to one controller. SCSI protocol allows com-

puter devices to talk to each other over simple cables similar to the way LANs do.

SCSI (Pronounced "Scuzzy") A technique for daisy-chaining a series of storage devices to one controller. SCSI protocol allows computer devices to talk to each other over simple cables similar to the way LANs do.

Seek Time. The time it takes the computer to retrieve data during a random access to a disk. Generally a function of the speed with which the read/write head can travel to the exact physical location on the disk's platter where the data reside.

Software. A program which translates instructions formed by carbon-based life-forms into commands that can be understood by silicon-based life-forms.

Software Hooks. Features in the operating system and BIOS that allow programs to share common code and data or use other programs for dynamic exchange of data.

Software Utility. A program that adds a housekeeping function not already supplied in the operating system. Many utilities are the kind that always operate in the background; they are called TSRs, or terminate-and-stay-resident programs. TSRs are usually moved into upper and extended memory to save space in core memory. Modern multi-tasking operating systems make TSRs obsolete.

Synchronous/Asynchronous Communication. Words used to describe how a device talks to another device. Synchronous communication requires that devices be paced by a separate clock-wire in order to transfer data. The bus concept is an example, also the parallel port connection for a printer. Asynchronous communication does not require an extra wire for the clock-signal, but is instead modulated on a radio signal which is used to synchronize communication. Telephone modems and serial ports on computers are this type of communication.

Upper Memory. Memory addressable above conventional memory but below extended memory. These addresses are used by BIOS, the video display, and other devices. Most systems have unclaimed space in this region. Memory managers are available to stuff programs normally intended for conventional memory into this loft area, to save conventional memory.

Virtual. Apparent, not real (whatever that is). Simulation by software of memory, devices, time and space. The software simply creates the illusion that something newer or better is happening, when it's just the same old stuff in a different package. Virtual events appear simultaneous or coincident only because the real events in the computer happen at electronic speeds (millions of events per second) in comparison to the ability of our brains to distinguish them at millisecond speeds. There are virtual machines, virtual memory, virtual reality (reality?), virtual addressing, virtual programs, etc.

Windows. An operating-system concept using graphic displays, virtual machines and memory, and full 32 bit data architecture. Programs appear in windows on the display. Each window is like a Chinese nested box and contains various dialogue boxes, scroll bars, buttons, icon functions, etc. Many software manufacturers use windows besides Microsoft. IBM, Apple, DEC, and NeXT have their own windows-type environments.

Workstation. An independent microcomputer on a LAN.

Computerized Clinical Information

Joseph W. Humphry MD*

Virna S.K. Cheung MBA

The use of computers for medical practice has not evolved as rapidly as might be expected. Even though MEDLINE searches are universally used for in-depth search of medical information, the effective use of computers in direct patient care has had very limited acceptance.¹ The Waianae Coast Comprehensive Health Center (WCCHC) has supported the development of an in-house computer billing and information system, Pacific Area Medical Manager (PAMM), that includes a Patient Health Status (PHS) module. Through local development of the system, physicians are involved in every level of planning the PHS. Acceptance of the computer system by physicians has increased.

The Waianae Coast Comprehensive Health Center is operated by the Waianae District Comprehensive Health and Hospital Board, Inc., a private, nonprofit corporation established in 1969. WCCHC has been in operation since 1973 and serves the residents of the Waianae Coast from Kaena Point to Makakilo. The basic philosophy of WCCHC is to provide quality health services to community residents regardless of their ability to pay.

On July 4, 1991, WCCHC implemented the billing and collection system—PAMM. The system runs on a Hewlett Packard 3000 mini-computer and currently supports about 90 users around the clock. Since its implementation, many new features have been added to PAMM based on WCCHC's needs, including a fully featured appointment-scheduling module and an evolving PHS module. The implementation of the PHS module is a major step toward the goal of incorporating clinical data into the overall system.

The PHS module is designed to maximize existing demographic and medical information used in the billing system and to minimize the need for clinical personnel to input data or to interact with the computer. It is developed in stages with the physicians involved in deciding priority areas to designing screen formats. It is directed toward improving medical practice by using selective information rather than replacing or duplicating the complete medical record.²

Computerized medical information soon will be essential to medical practice. An example of the current use of the PHS describes the process and the principles involved in the system's development: Control of hypertension slows the devolution of diabetic nephropathy; effective control is important in delaying the onset of renal failure.³ The U.S. Indian Health Service (IHS) recently completed a chart audit review of the care of diabetes including an assessment of the control of hypertension.⁴ WCCHC carried out a similar study using data captured in the PHS vital-signs file.

Methodology

The vital signs—blood pressure, weight and blood glucose—have been recorded at WCCHC in patients with hypertension or diabetes since 1992. The average blood pressures for the most recent 3 visits were calculated for all patients with diabetes. Data on patients with fewer than 3 visits was entered and the sex and age were extracted from the demographic information in the billing system.

Results

A total of 469 patients with diabetes were evaluated, and the cohort included 55% men and 45% women. Analysis of the data indicated that 39% of the patients had blood pressures >140/90. A complete breakdown according to the level of blood pressure control is shown in Table 1.

The number of patients with poorly controlled blood pressure increased from 13% in those under 35 years of age to 61% in patients over 75 years of age. Table 2 incorporates these data. Table 3 shows the breakdown according to the number of visits. Only 15% of the patients with diabetes had a single visit; the majority of patients had 3 or more visits.

Discussion

The findings generated in a short time on the computer indicate 39% of the population with diabetes at WCCHC have poorly controlled hypertension similar to the IHS results.¹ Previous evaluation by the Hawaii State Diabetes Control Program of the Waianae population with diabetes estimated that 60% of patients with diabetes also have hypertension. An estimated two-thirds of patients with diabetes had inadequate control based on outcomes.⁴ Half of those who failed to reach the 140/90 blood pressure level were in the group with systolic blood pressures between 140 and 150. Since the principal objec-

TABLE 1: Patients with diabetes who have elevated average blood pressures.

Blood Pressure	Patients With Elevated BP	Percentage
135/85*	246	52
140/90*	184	39%
140	168	36%
150	92	20%
160	39	08%
170	18	04%
180	08	02%

*Either systolic or diastolic blood pressure elevated over this value

tive of our study was to discuss the medical application of the computer, the actual results of the study will not be discussed further.

In contrast to that done by the IHS, our computerized PHS allowed for 100% sampling. Chart reviews are time consuming and results then need to be entered into a computer for any complex analysis. By having the raw data stored in the computer, we were able to store and reproduce the data with little investment of time and to give feedback to our clinical personnel pertaining to the treatment of hypertension in patients with diabetes.

One of the principal reasons why WCCHC supported the development of the PAMM system was to have available the link between the PHS and the other functions, such as claims processing, scheduling, and reporting. Similar to the computerized "mini-record" reported from North Carolina⁵, our system is being developed in stages according to priorities. This approach is in contrast to many systems that have attempted to capture the entire medical record.⁶ PAMM captures the medical information that will directly affect patient care as well as evaluating the provider. Capturing the

(Continued) ►

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entire medical record on the other hand required acceptance by all the providers of a completely developed program that met the needs of all who use the medical records.⁷ By using data captured in the billing system, our PHS module collects data with a minimal amount of superfluous entry. The way the program is structured permits the insertion of new data sets linked to existing data sets with minimal change in the core program; this allows the PHS module to be developed in successive stages.

The vital signs file, developed to track the outcomes of treatment of patients with hypertension and diabetes, required new blocks (fields) for blood pressure, blood glucose, weight and height on our encounter form. The nurse records vital signs at the time of encounter; this is entered into the computer for billing. Any patient seen for diabetes (ICD-9 codes 250.0 to 250.9) has weight and blood-glucose recorded; those who also have hypertension (ICD-9 codes 401.0 to 401.9) have those data entered. The encounter forms that do not have the required data are rejected by the computer and returned to the nurse for completion. Our staff rapidly learned to complete encounter forms correctly to avoid the hassle of having the forms returned.

We currently are introducing immunization history and health maintenance information (periodic screening-mammography, Pap smear, stool guaiac, sigmoidoscopy, physical exam, EKG, eye exam, etc.) on all patients into the computer. The billing system has been using specific CPT codes for specific preventive services. Using these codes and the concomitant dates of service from the

TABLE 2: Patients with diabetes with high blood pressure (HBP) systolic >140 or diastolic according to age.

Age	HBP	Total	%HBP
<35	8	60	13.33%
35 - 44	19	70	27.14%
45 - 54	56	127	44.09%
55 - 64	47	111	42.34%
65 - 74	37	73	50.68%
>= 75	17	28	60.71%
total 469			

TABLE 3: Evaluation of patients with diabetes and hypertension by the frequency of visits.

Number of Visits	Patients with HBP	Total Number of Patients	%HBP	Average Age
1	22	69	31.9%	47.73
2	17	55	30.91%	51.15
3 or more	145	345	42.03%	54.17

existing billing information of the last 5 years, we were able to construct health-maintenance data files. Active collection of other data by the clinical staff is required only when it is needed. At the time of the encounter PAMM identifies patients who need immunizations or preventive health measures. It eliminates the need for the nurse or the physician to seek that information from the patient or the chart. "Flagging" for certain items has to be entered into the computer by a nurse or physician.

Current projects include developing a patient problem list, a perinatal and family planning tracking and outcome system, and the additional use of the vital-sign file (height and weight) to measure pediatric growth and development. Future projects include the addition of files of laboratory data and of lists of medication.

Physician acceptance of the PHS is essential. They need to see

clearly the clinical value of the computerized data in order to further the process. Previous studies have demonstrated acceptance by providers when they feel patient care is improved by this means⁸ and improved overall care as instant reminders for preventive health care show up on the screen.⁹

The PHS system is designed to provide important information to the physician about the patient with minimal disruption of patient care. The providers do not actually have to interface with the computer, but are trained to use the on-line information of the PAMM system if they are interested.

With the development of the PHS, quality assessment of care at WCCHC will be strengthened. The measurement of practice patterns and medical outcomes by this process can be expected to replace current quality-assurance programs based on limited chart audits and peer review, a method that recently has come under critical review.^{10,11,12} The report to the providers regarding the control of hypertension in patients with both diabetes and hypertension is intended to have an impact on patient management. Serial reports will provide feedback to clinicians as to therapeutic progress and whether this technique will improve patient care.

We are rapidly expanding our use of PAMM in the area of quality assessment. Developing an effective quality assessment program not only improves patient care, but is increasingly important to the purchases of care and to consumer groups.

Conclusion

PAMM with PHS has some unique features that allow the providers, the users of the system, to deal with the rapidly changing aspects of medical care. Local innovative developments not only allow for programs sensitive to local needs, but also speed modification of QUEST, the revamping of Medicaid reimbursement. The system is designed to develop a quality-improvement program based on selective measurements of outcomes and practice patterns, rather than by limited case reviews or existing peer review programs.

Acknowledgments

We gratefully acknowledge the assistance of Alan Chun MD and Cedric Yoshimoto MD in making this report.

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Informatics in Medical Practice: Billing Systems Survey by the Hawaii Medical Association

Randolph K.M. Wong MD*

The Information Age has arrived! Our offices are quickly integrating information machines for the business part of our profession, just as the stethoscope and scalpel are requisites for the practice of medicine and surgery. The mission of the HMA Computer Committee is to provide guidance in the direction of medical informatics for its members. We hope to assist the membership in the selection, evaluation and use of the products relating to the processing of information in the modern practice of medicine.

During the spring of 1992, the committee set out to poll the HMA membership on their use of computerized billing systems. It was our intent to discover what was available and to examine the differences in the various billing processes in order to provide a comparative study for the membership. The results of this survey are presented here for your perusal. The questionnaire was mailed to the entire membership census of 1,750. Forty-seven responses were received from offices and from nonphysician vendors, representing 218 physicians for a response rate of 12.45%. When the vendors who filed questionnaires were excluded, 36 physicians responded (2.06%).

The low response rate must be taken into consideration when interpreting these data and statistical significance cannot be implied. It also is important to interject that there have been many changes in this industry since this poll was taken. These products have likely changed or been upgraded to keep up with changes in the health care environment. However, the data do provide a snapshot of what was available and in use during the spring of 1992.

The responses demonstrated a dominance of IBM or IBM-compatible microcomputer systems. Microsoft DOS, or a compatible operating system, was also in the majority. One system was using UNIX; several were networked with Novell Netware. There were no Apple- or Macintosh-based systems reported. There were no responses from mainframe systems although one vendor who was interviewed, Praxis, offers a multilevel platform information service integrated with the office billing system.

Figure 1 represents a breakdown of the returns submitted by the end-users (either the physicians or their office staff) and by the vendors of the various software products; we had requested that the person most familiar with the information system complete the questionnaire. Although we were referring to the end-user in the office staff, it was apparent this

person wasn't always the most technically knowledgeable about the software or hardware specifications. Many of the offices quickly tossed the questionnaire over to their vendors. It could easily be determined that there were a couple of vendors of products who readily filled out the questionnaires for their clients. The vendors often chose to collect the questionnaires and submit one to represent their clients collectively. Although this might indicate an additional support service provided by these vendors, the relative distribution shown should not be taken as representative of the distribution of products in our community.

Because we wanted to get an idea of customer satisfaction with the use of these products, the remainder of this study deals only with those questionnaires submitted exclusive of the vendor provided information. Figure 2 shows the break-

(Continued) ➤



Randolph K.M. Wong MD

Physicians Represented HMA Computer Committee 1992 Survey

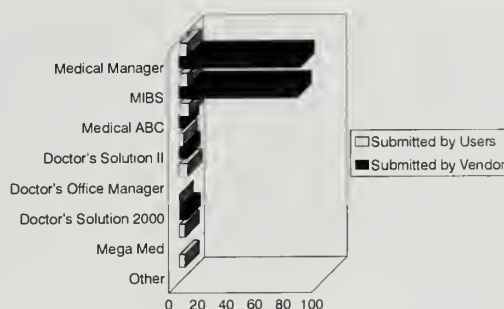


Table 1

User Responders

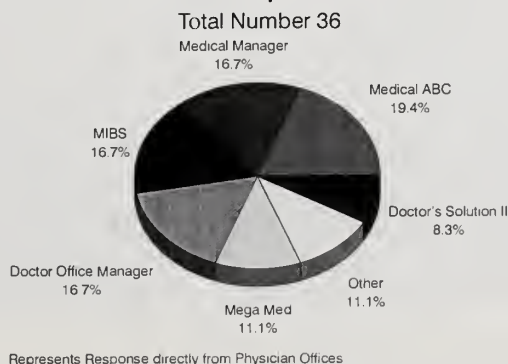


Table 2

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Honolulu, HI 96814

(Continued from page 327)

down of billing products from the 36 user-submitted questionnaires. Again, these numbers do not provide any significant statistical confidence but are being presented for purposes of information only. It is interesting that the user-submitted responses were fairly evenly distributed over 6 products. These products were then chosen for the comparative evaluation that follows.

The average reported cost for the software and hardware is shown in Figure 3. Some of the responses were necessarily subject to special interpretation as the total cost of the package was occasionally submitted. However by scanning the responses, it was somewhat obvious which numbers were the appropriate ones to determine accuracy. These numbers represent the purchase price of systems over a period of time when significant changes in cost occurred as technology advanced. What one office might have paid several years ago might not be exactly the same product that another will buy tomorrow although the product could be under the same name. Software upgrades, higher hardware requirements, changes in levels of technical support and training could serve to change the price or value of a product. The evolution of the microcomputer processor has fueled an incredible industry over the past decade. What one office bought years ago is likely to be nearing obsolescence; the office might be looking toward a series of both software and hardware upgrades more and more as technology, health

care and governmental regulations continue to evolve.

The high and low range of system costs are presented in Figure 4. These costs vary because of user-options as well as vendor-recommended configurations for the various needs of the medical office. Some systems are appropriate for the solo practitioner and should be available at the low end of these ranges. Many of these systems are excellent for small groups or partnerships and can effectively have their cost spread over several physicians' practices. The high-end systems are in those offices that have opted to install networked computing terminals or personal computers (PC). Those costs also could have included other peripheral devices such as printers, modems, fax boards, and other software not specific to the billing.

Figure 5 shows that in early 1992 most of these systems were operating with hardware that now are considered to be obsolete by today's PC standards. Yet it is reassuring to know that the older hardware still can be useful. It is likely that the current system configurations are being installed with 486 microprocessors, at least 2 generations beyond those presented here, and with a minimum of 2 to 4 megabytes (MB) of random access memory (RAM). It also is likely that the current versions of the software have increased their program and data-space requirements.

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Average Reported Costs

1992 HMA Computer Billing Survey

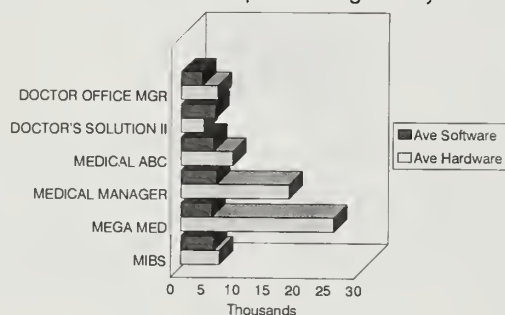


Table 3

Minimal System Requirements

In Use as of May, 1992

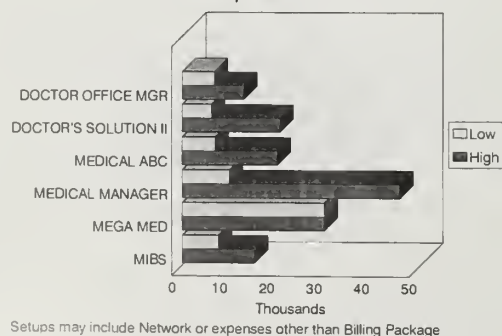
Program	Processor	RAM (KB)	Program Files (MB)	Data Files (MB)
Dr. Office Mgr.	286	640	6	30
Dr. Solution II	286	256	7	30
Medical ABC	286	640	2	9
Medical Mgr.	8088	512	2	3
MegaMed	286	640	5	n/a
MIBS	8088	512	2	40

Current application requirements have likely been upgraded

Table 4

Range of System Costs

Software plus Hardware



Setups may include Network or expenses other than Billing Package

Table 5

Modification of Software

Can it be Customized?

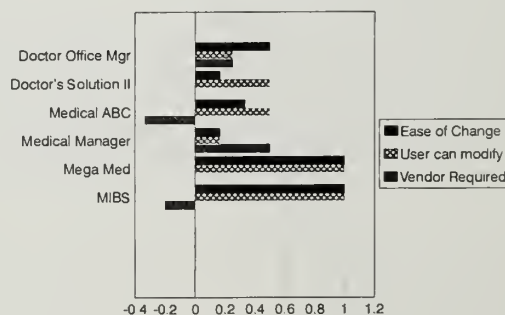


Table 6



"Ron's Rule—I give myself one week to meet new people and start having fun on a locum tenens assignment. It hasn't failed me yet."

Ron Richmond, MD, joined the CompHealth locum tenens medical staff when he completed his residency. He wanted to travel. He loves to meet people. A little time off sounded really good. And he thinks being exposed to different types of medical practice will serve him well when he returns to his hometown to establish a community health center.

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(Continued from page 328)

The next series of figures were determined by weighting the responses to specific questions. Weights were based on the user's perception of features of their billing system. We acknowledge that variability in technological aptitude, computer literacy, and experience with use of the system are difficult to evaluate. Some of the responses indicated an inability to

understand the questions asked and many questions went unanswered. When compiling the data, unanswered questions were considered neutral with zero weight (0). Affirmative answers were granted a positive weight (1) and negative answers were considered negative (-1). The answers were then averaged with regard to the product group and presented in the following charts. The highest degree of agreement is represented by the value 1.0, the lowest value of -1.0 represents the negative response.

Modification of the software (Figure 6) pertains to the ability of the product to be customized to accommodate changes in the fee structures and to accommodate coding changes. This feature usually can be performed by the user on a limited basis by defining default settings or choosing options offered by the software. The degree of modification required depends in part on the willingness of the user to accept the features offered. If the software does not support an essential function, either the office must change to accommodate this flaw or the vendor must modify the product, which might make it difficult to upgrade later.

Claim-completion (Figure 7) requires that the billing system complete the top half of the HCFA 1500 correctly with the proper format (ie, patient's last name first). The system should allow for additional options of format for unique forms (ie, Medicaid, Blue Shield). "Four dx" per-

Claim Completion

Accuracy in filling out claims

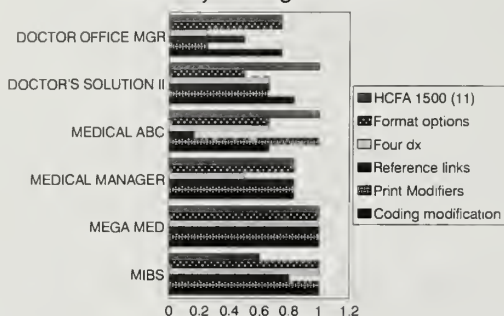


Table 7

Accounting Features

Perception of Versatility

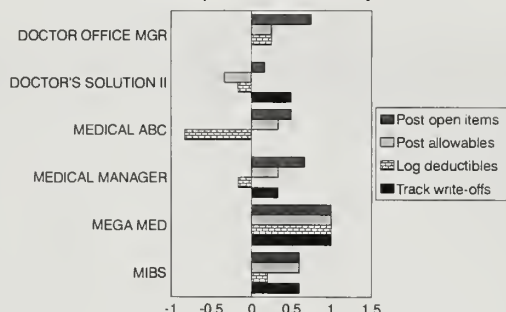


Table 8

Editing of Fees

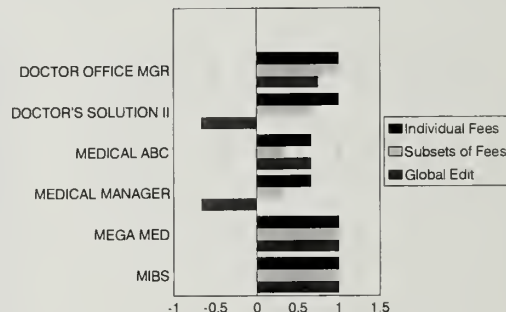


Table 10

Claims Submission

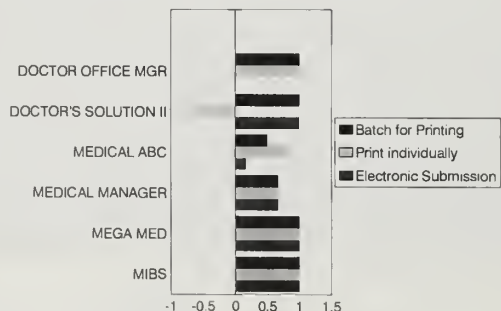


Table 9

Revenue Breakdown

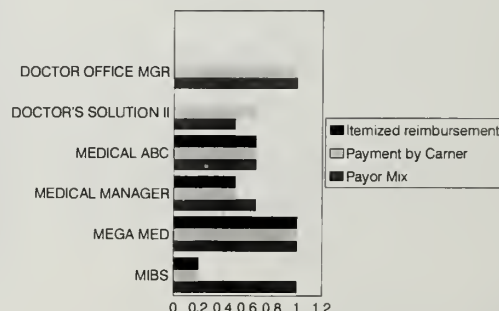


Table 11

the spreadsheet. As the name implies, spreadsheets are electronic versions of paper worksheets. The difference is that they support the user with a full library of powerful data operations and mathematical functions. They also are versatile in receiving input data, modifying the data, and transferring the resulting output data, making them extremely useful with other applications. This makes the spreadsheet a powerful tool for designing forms, creating data bases, and performing calculations on large amounts of data.

Common uses for spreadsheets are inventory projections, project budgeting, and capital investment analysis. They also are suitable for handling statistics and generating demographic information from large amounts of raw data. In its simplest form the spreadsheet can serve as a very powerful desktop calculator.

How to Save Time When Working on More Than One Computer

Sharing information between 2 computers usually involves making a copy of the information on a diskette or diskettes, carrying it to a different computer, and copying it from the diskettes onto the new computer. Computer "nerds" are thus seen frequently hauling little piles of diskettes around with them.

Since the information is electronic, it can be sent over a communications line. If 2 computers are connected by a line they can "talk" to one another; this can be accomplished by connecting both machines with telephone lines. However, the quality of the signal that is transmitted over these lines is modest at best and the subsequent transmission therefore must be very slow.

The use of cable similar to TV cable (coaxial cable) allows greatly improved quality and much higher transmission rates, resulting in a quicker, cleaner communications link.

Linking computers together in this manner is called networking and essentially eliminates the need to tote diskettes around within an office environment. In addition, it is possible to operate a program that resides on one computer, from a different computer that does not actually have that program. To the user the program will appear to "virtually" exist and run on his or her machine, though it physically resides elsewhere. It also is possible for a user to initiate and control a program on another computer from his or her computer without disturbing the user on the other computer. This level of networking is a form of robust connectivity and greatly facilitates the ability of work groups to perform both as a team and independently within an office environment.

The formal networking of computers has been a nightmare in the past with the learning of a new networking language and huge headaches with communication "protocols". However, networking is coming of age, with each subsequent generation becoming more user-friendly. A friendly form of networking software is already included in the Macintosh System 7 operating system. Complete networking capability is an integral part of the Windows for Workgroups software package, with no special knowledge required to use it. Other network software is becoming easier to

use as well, but generally requires an individual with some knowledge who becomes the "network administrator". The simplest form of networking supports file sharing. This enables a physician to quickly scan patient registration information located in a file on the receptionist's computer. More sophisticated support allows multiple users to access and work on the same file at the same time through 2 or more computers (receptionist and billing clerk, for example). The larger the office, the more helpful these features become.

The networking of a small office can normally be performed in one day. Typically a morning is spent running the necessary cables to the various node sites and installing the required communications cards in each computer. The software installation and system configuration then can be performed in the afternoon. (An example of a small office network is illustrated in Figure 1.) Once the system is connected, user accounts are assigned, security programs are initiated, and sharable resources, such as printers and certain

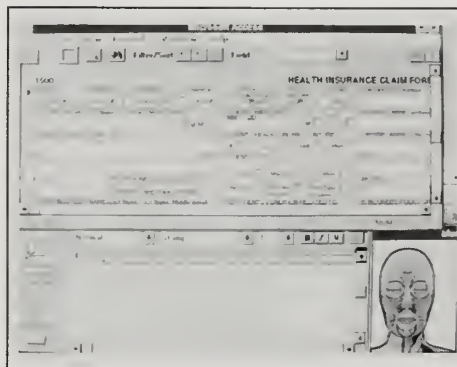


Figure 2: Multi-tasking with Windows 3.1.

The active window shows the Access data base manager running an insurance data entry form. Patient information entered through this form will be stored in the general patient data base. Below the Access window is an MS Word window and its document. In the lower right-hand corner of the screen an anatomy program is displaying a muscle diagram for the face. Background utility programs are visible in iconized (reduced) form in the lower left part of the screen.

data base files are set up. These features allow a user to "log on" to one machine, generate documents through a second, and print the results on a printer connected to a third. At all times the system security feature will ensure document integrity and confidentiality.

How the Computer Saves Time in Medical Searches and Fax Messages

Most physicians are aware of the vast resources available for searching for medical information by modem, a device that enables the computer to communicate with a remote computer site over telephone lines. Some modems can be connected to a computer externally while others are installed internally. The Honolulu Medical Library and the National Library of Medicine both offer services that allow literature searches from virtually any computer. Similar levels of support for information retrieval are offered by government and private agencies, and academic institutes throughout the world. Most of these agencies and institutes are accessible through the worldwide Internet system. Software for taking advantage of these services is quite easy to use and very helpful. In many cases enhanced, standard specification or public domain software is used by the service to greatly facilitate information search and retrieval requests. These enhancements are normally available on diskettes or by electronic downloads, either free or for a small fee.

Most current modems also support facsimile transmission

(Continued) ➤

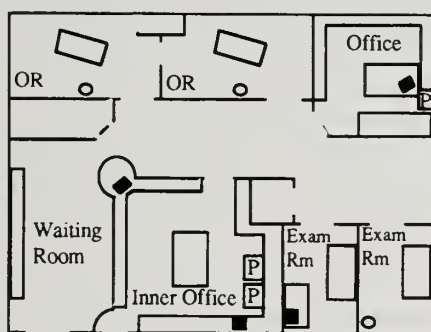


Figure 1: Typical small office network. Four computer stations (black boxes) and 3 printers (Ps), are linked by coaxial cables in the ceiling. Three future stations are indicated by small circles.

protocols. A computer connected to such a modem now can act like a fax machine. Documents can be sent out from a variety of programs and incoming fax messages can be stored in files on the computer's disks. These functions can be performed in "background" mode, allowing the computer to be used normally with other applications. Once a facsimile is received, optical character recognition (OCR) software can be used to clean up the document and convert it into a standard word processor file. Once in this form, the document can be resent either as a file, by modem transfer or as a facsimile image.

Keeping Tax Records with the Computer

Anyone who does not use Quicken or a similar checking account program does not know what he or she missing. These programs offer much more than simply balancing the checkbook. After entering the checking information, a large number of reports can be generated, including all of the information needed for income tax filing. Accountants probably will have already recommended the use of these small, yet powerful application programs; they make it much easier to track office overhead expenses, profits and losses, and all forms of daily accounting data. They also provide an easy way to keep your eyes on the books.

Using Quicken to write checks ensures that the user always knows what transactions are being made in the accounts. Reconciliation becomes an almost automatic functional operation, making it easy to verify that the numbers match up. Detecting errors caused by the bank or by office staff can be done in a few minutes, instead of hours. An up-to-the-minute accounting also is possible. An alternative to Quicken is Microsoft Money, which offers similar functions and features. For more advanced accounting capabilities, full accounting packages similar to the PeachTree Accounting series are recommended.

A Generic Processing System Recommendation

Hardware—Windows-based systems running on 486-based computers currently are the most cost-efficient solutions. Powerful, fully configured systems can be purchased for under \$2,000. The system should have at least 8 bytes of RAM (it will run much slower without this upgrade) and 200 MBytes of hard disk. It should include a fax-modem card and a backup device (tape drive, cartridge storage device, etc.). A CD-ROM drive is a nice addition that is becoming an essential system component; if not purchased with the system it can be added later. Macintosh microcomputers, Sun workstations, and other systems offer wonderful

alternatives, but they tend to be more expensive. *Do not buy a computer with less than 8 Mbytes of ram, less than 200 Mbytes of hard drive, and a graphics accelerator card for the monitor. Do not buy a monitor with a pixel display greater than .28 mm pitch. Upgrades are inevitable because the resolution will be insufficient.*

To enhance a system further, consider investigating the capabilities and advantages offered by any of the following components and peripheral devices.

Optional Equipment:

- Scanner
- CD-ROM reader
- Laser printer
- Color printer
- Video capture board
- Multimedia cards
- Bar code scanner

Software—To properly support the plethora of application software available on the market today, reliable operating system software must be used. At present the most comfortable environment for 486-based machines is the combination of DOS 6.0 used with Windows 3.1. IBM's OS/2 software is very good and offers some advantages to the DOS/Windows option, but requires large amounts of disk space to properly support. (For the Macintosh, the System 7 operating system offers a wide range of capabilities in a comfortable user environment).

Currently all of the popular microcomputer operating systems offer some level of multi-tasking; the ability to perform more than one task at the same time. True multi-tasking, the ability to run multiple programs, not only will depend on the operating system, but also the design of the application programs. All Windows-based and OS/2-based software are designed for multi-tasking environments. Figure 2 illustrates a situation where 3 application programs are running concurrently. In addition, there are several utility programs running in the "background".

The following Table lists the major application categories and corresponding program recommendations. In addition, a secondary list offers viable alternative programs for each application category.

Alternatives—Each of these options represents a solid choice from among several excellent alternatives in its class. They are given as a basis for forming a good system, and to minimize complications during the set up period. All of these programs can exchange data with other popular competitive products. Other choices would work, and might even be preferable for some situations. For more information about these competitive products and their advantages and disadvantages, contact your local computer stores and refer to any of the several informative computer magazines now available.

How to Do It

Buy the computer as fully configured as possible. It might cost a little more to get the exact system you want, but the amount of time and trouble it will save are well worth the extra money. Novices should buy from a local vendor and have the system set up and tested. Again, the slight additional cost will save hours of aggravation. (If you want to learn about computers in addition to using them, buy components through a local distributor or through the mail and try to set them up yourself.)

Application Software—M.S. Windows 3.1 running on M.S. DOS 6.0 or higher.

Application Category	Recommended Program	Alternative Program
Basic Accounting	• Quicken	MS Money
Word processing	• MS Word	WordPerfect
Data base management	• MS Access	Paradox
Fax communications	• Winfax Pro	FaxGrabber
Networking	• MS Workgroup for Windows	Lantastic
Spreadsheet	• MS Excel	Quatro Pro

Total estimated system cost: approximately \$3,000.

After setting up your computer (including windows), install Word, Access, Quicken and Winfax. This is easy to do. Simply insert the diskette labeled "Install" and follow the directions. It takes about 30 minutes to install these programs. Next, learn a little about how to use each of these programs. Each comes with a tutorial that takes an hour or so to do. Once you are familiar with the way the programs work, you can start to use them.

Start using Quicken to enter your checks immediately. If you like, you can get Quicken checks from your bank, which is often cheaper than buying them from other sources. This is particularly useful if you have an extra printer or if you do all of your checks in batches. Otherwise the time lost in changing the paper in the printer is greater than the time saved by having Quicken write the checks.

Start using Word to do simple correspondence and short reports. Experiment with Word's insertion capabilities to install simple diagrams, tables, and even equations into your documents. As you become more sophisticated, you will discover how easy it is to customize your documents to produce a personalized style and a professional appearance. Templates can be designed that can be used to facilitate the rapid distribution of personal and professional correspondences. A more advanced option is to pre-program functions (creating "macro programs") to automatically generate required documentation on request. Fantastic amounts of time can be saved by customizing these "macros" to your personal situation.

Set up Winfax to receive in background for your faxes. This will save money and time on fax paper, space, and machine costs. Facsimile transmissions then can be initiated from the Winfax environment or from the Word environment after the document has been created.

Start to use Access to initiate the filing of medical claims; it

also can be used for patient registration. This will provide the generation of an electronic mailing list of patients. If the data is entered at the time of registration, it will be there for use when each claim form is filled out. Designing the data base is a bit tricky and may require some assistance from an experienced data base expert or consultant. [Call or write for information to obtain a free copy of a soon-to-be-available medical data base.] Access is fantastically flexible and can easily be customized to the individual needs of any office. It is also an incredible deal: Originally projected to cost \$795, it is currently available for \$89 because of competition with Paradox (Borland International), another excellent program. We favor Access at this time because of its tighter integration with Windows.

Conclusion

With a new generation of inexpensive, but powerful processors and user-friendly software, every medical office now has the opportunity to reap the benefits of the information age. Whether to reduce the administrative and bureaucratic workload or to enhance actual medical applications and procedures, computer support in the office is rapidly evolving from a luxury to a necessity. By utilizing off-the-shelf hardware and software, and with a little creative imagination, tremendous improvements in office efficiency and overall business operations are obtainable. This discussion has only scratched the surface of what capabilities are possible. In most cases, only the user's imagination sets the limits for office automation.

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Tripler Pioneers Telemedicine Across the Pacific

Calvin B. Delaplain MD*

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Between January and August 1993, 59 medical teleconsultations were conducted successfully between the video teleconference center at Tripler Army Medical Center on Oahu and the video teleconference center on Kwajalein Atoll in the Republic of the Marshall Islands. This pioneer effort in the Pacific connected 2 archipelagoes separated by more than 2,200 nautical miles. Diagnostic and therapeutic decisions were made in the specialties of orthopedics, dermatology, radiology, urology, pediatrics, ophthalmology and physical therapy. Geographic isolation no longer means limited medical specialty care.

Introduction

In January of 1993, the Commanding General of Tripler Army Medical Center (TAMC) went to Kwajalein Atoll accompanied by a team of Tripler physicians. They had 2 goals: To treat patients on the atoll and to explore the use of telecommunications in order to extend the practice of specialty medicine across the Pacific. A few telemedicine projects had been started on the Mainland, but this represented a pioneering effort in the Pacific Ocean.¹ On that day, a satellite link was established between the video teleconference centers (VTCs) on Kwajalein and TAMC. Kwajalein's physicians and the visiting TAMC specialists presented 3 patients with different skin diseases and 2 separate radiographs for evaluation by consultants assembled at the TAMC VTC studio. All 3 skin conditions were correctly diagnosed and both radiographs were correctly interpreted. Since this initial trial success, TAMC has rapidly capitalized on its in-house VTC capability.

Background

Kwajalein is a large atoll in the Republic of the Marshall Islands; it is used as a missile research facility under the United States Army Space and Strategic Defense Command. A population of approximately 3,000 people consists primarily of American workers under contract to the Department of Defense.

At present, medical care is provided under a contract with the Army. Five physicians trained in the fields of family practice, emergency medicine and general surgery handle all patients

including those who would normally require diagnosis and therapy by a specialist. The only option previously available was to evacuate the patient to Honolulu which was costly in both money and time. Now a new option of telemedicine was being offered.

Methods/Equipment

Tripler AMC has a DCTN (Defense Commercial Telecommunications Network) studio with three 17-inch television monitors and 3 video camera systems. The studio seats 10 people and can expand to handle about 20 if necessary. A slightly larger but similarly equipped studio is on Kwajalein. Both studios have stands for graphics to hold digitalized analog images. Prior to the consultation, the Kwajalein physician reviews the format of the videoconference with the patient.² The patient (and family members in some cases) is brought into the Kwajalein studio and

seated before a large screen monitor where he or she is able to see and speak with the Tripler consultant. Each teleconsultation typically begins with an introduction of the patient and of the TAMC consultant. The attending physician on Kwajalein gives a brief synopsis of the case and the patient can augment the history and present special areas of concern if he or she wishes.

The consultant at TAMC can suggest physical examination maneuvers and request close-up views of any pertinent skin findings. A graphics stand is used at both sites for high-resolution transmission of radiographs, lab sheets, EKGs, and other physical data.

Results

To date we have had success in 7 different specialty fields:

Dermatology: Patient history and video examinations have almost always been sufficient to generate a satisfactory diagnosis. The clarity of resolution and color in the monitors have enabled us to make the diagnoses of skin conditions as diverse as Margarita-lime contact dermatitis, basal cell carcinoma and



Figure 1: Tripler's VTC center "live." Left TV monitor shows Kwajalein patient to the left of Dr. Jim Troxell (General Surgeon on Kwajalein). Seated at the table in the foreground, from left to right are TAMC specialists Dr. Scott Norton (Dermatology) and Dr. Tim Winslow (Cardiology). The broadcast technologist, Mr. Todd Tanaka, is seen at the control console.

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neonatal acne, to name just a few. Occasionally the presenting physician has been asked to supplement the transmitted images with observations regarding the *feel* of a particular rash or lesion.

Orthopedics: These specialty consultations have been immensely helpful in deciding whether referral off-island is necessary. Diagnoses and treatment options have involved entities as varied as deltoid ligament sprain and *rectus femoris* contracture. Acute injury, post-reduction, and in-cast radiographs are easily interpreted and are an essential part of all orthopedic teleconsultations.

Radiology: Most routine bone films can be read without difficulty, but because television monitors do have limits in resolution, we cannot read chest radiographs beyond a preliminary viewing and usually request the films be sent to TAMC for final interpretation. This is especially important when looking for subtle abnormalities such as nodules, interstitial disease patterns, pneumothorax, etc. Clearly, there is a need for a dedicated high-resolution teleradiology/PACS system for networking in the Pacific.³

Ophthalmology: We have had surprising success in viewing the cornea with and without fluorescein dye. Our ophthalmologist is enthusiastic about continuing further teleconsultations in the case of external eye disease.

Urology: The teleconference has been used to provide recommendations concerning risks of cancer after vasectomy and in options for therapy in the case of a failed vasectomy. The video conference has been a satisfactory medium for a urologist's review of IVP studies.

Pediatrics: The teleconference also can be used for counseling sessions. We had a reassuring visit with first-time parents alarmed by their baby's excessive regurgitations after breastfeeding.

Physical therapy: We have encountered unexpectedly superb success in teaching both health-care providers and family members in directed physical therapy procedures.

Discussion

We have learned through this pioneer effort that telemedicine is basically a win-win situation. After the successes in every field we tried, we now know that geographic isolation no longer means limited medical specialty care.

The *patients* benefit from having the knowledge and skills of medical specialists readily available. Initially we thought there would be hesitation on the part of the patients to be subjected to a physical exam on TV, but now many patients request evaluation by video in order to avoid long and expensive medical evacuation. There is a little ham in everyone, both young and old! An informal survey of patients' impressions indicate there is almost the same closeness and immediacy in the teleconference setting as in the regular doctor-patient encounter in an office.

The *remote health care providers* benefit from the learning experience. Each video teleconference offers a unique, case-based, medical education opportunity. Although its hard to quantify, specialist confirmation of diagnoses and treatment options is valuable for any general health-care provider working in an isolated environment.

Ultimately, Tripler Army Medical Center benefits by being able electroni-

cally to extend its medical services to distant beneficiaries and to gain visual access to varied tropical diseases as they evolve.

The Future

Our experience with medical video teleconsultations has proven that in many cases it is far more efficient to transmit information electronically than to physically transport patients or specialists. At least 15 air-evacuations have been avoided since the beginning of our project and the cost of each trip has been estimated at \$2,000 (travel and lodging). Obviously it doesn't take long for the system to pay for itself! Even in cases where it was concluded that referral to Honolulu was indicated, the teleconference facilitated ordering special tests, procedures and appointments in advance. The Tripler Telemedicine Committee is committed to extending this cost-effective technology to our beneficiaries in other remote sites of the Pacific Basin. We would like to involve more TAMC health-care specialists, and finally we would like to establish closer ties in these endeavors with the University of Hawaii John A. Burns Medical School, the Veterans Administration, and the other uniformed services such as the U.S. Navy, Air Force, Marine Corps, Coast Guard and the Public Health Service.

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Consent and Privacy in Telemedicine

Scott A. Norton MAJ, MC*

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The electronic broadcast of a medical interview, or a videoteleconsultation (VTC), challenges many of our traditional concepts of privacy and confidentiality. The nature of a doctor-patient relationship changes dramatically when the open airwaves carry the personal histories, images, and concerns of a patient. Discussions of telemedicine often allude to inherent ethical concerns yet there are no established guidelines for the ethical conduct of a VTC.

Introduction

During the past year, we have conducted more than 70 VTCs¹ and have paid attention to aspects of VTCs that pose ethical challenges. Without claiming any special expertise in medical ethics, we describe in this article our efforts to preserve private, confidential relationships between patient and physician during a VTC.

Confidentiality

Patients who appear on VTCs must be informed that aspects of the relationship with their physician have changed (Fig 1). The physician maintains his responsibility to keep patient information confidential but the customary total privacy and confidentiality of the medical setting cannot be guaranteed. The patient's image and medical history are conveyed not only to the consulting physician but, by necessity, to several individuals outside the traditional medical team. The broadcast procedure requires technical staff at both ends and frequently we have observers interested, not in the particular patient, but in the practice of telemedicine. In small communities, it is possible that the patient knows the nonmedical personnel socially, compounding the sense of loss of privacy.

Furthermore, transmission over the airwaves or by direct link is not secure—ie, others can intentionally or unintentionally gain access to the broadcast. Some centers now scramble their broadcasts electronically to ensure confidentiality. The military's technical personnel often have security clearances and are accustomed to handling sensitive information. In general, however, the implicit code of ethics of professional video-broadcasters should be an assurance of confidentiality.

Intimacy

Most patients and physicians want warm professional relationships with each other; therefore, important for the consultant to appear as personable over the video as he or she might be in a face-to-face setting. Bright lights, technical contraptions, and extraneous personnel can diminish this feeling; we advise conveying to the patient an image of the consultant alone, free of background clutter and motion. Keeping the consultant's studio free of distracting clutter helps convey the impression that the consultant's sole purpose is to evaluate that patient, adding to the sense of intimacy.

STATEMENT OF UNDERSTANDING FOR VIDEOTELECONSULTATIONS

I understand the following:

1. Details of my medical history, examinations, X-rays, and tests will be discussed with off-island specialists.
2. Limited physical examination may take place during the VTC.
3. Nonmedical technical personnel may be in the VTC studio to aid in video transmission.
4. Other medical or nonmedical personnel may be off-screen at the consultant's VTC studio as observers or technical assistants.
5. Video recordings may be taken of the VTC and may be viewed by various personnel for training and administrative purposes.

Noting all of the above, I understand that participation in the medical VTC constitutes a waiver of the usual rights to doctor-patient privacy.

I further understand that I have the right to:

1. Request that USAKA's VTC physician omit specific details of the history of examination that are personally sensitive to me.
2. Limit any physical examination proposed during the VTC.
3. Request that nonmedical USAKA personnel leave the VTC studio at any time.
4. Request that all USAKA personnel leave the VTC studio to allow a private consultation with off-site specialists.
5. Stop participation in the VTC at any time.

Signatures of counseling physician:

Witness:

Patient or Parent/Sponsor/Guardian:

Date and time:

Figure 1: Information and consent form used by the Kwajalein Hospital, Kwajalein, Republic of the Marshall Islands. Most patients at this hospital are American citizens working for the U.S. Department of Defense or its contract agencies. VTC = video teleconsultation; USAKA = United States Army Kwajalein Atoll.

We recommend that the consultant's studio resemble a typical physician's office. We are fortunate that our studio allows the consultant to sit behind a solid wooden table. The table is clear except for a nameplate, paper, and pen. When patients are involved in the unfamiliar process of telemedicine, they are reassured to view the consultant the same as in a traditional setting.

A nameplate listing the consultant's name, degree, and specialty adds credibility, familiarity, and helps the patient remember the name of a specialist whom they have never met in person. Similarly, the consultant must try to address the patient using only the first name, in an attempt to prevent a depersonalized relationship, yet preserving some anonymity.

Privacy

Although the patient has waived the usual rights to privacy (Fig 1), a properly conducted VTC should nevertheless be a private session. That is, it should be free from disruption, intrusion, and should avoid a fishbowl atmosphere.

First, the image broadcast to the patient should show only the consultant. It is disruptive and unnecessary for people to stray

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into the camera's field behind the consultant. The patient must be informed that there could be people off-camera in the consultant's studio who are observing the session. Nevertheless, the patient can expect that the consultant is the only individual interested in the medical details of the case. If an observer off camera at the consultant's end needs to be called-on for an additional opinion, the patient should be so informed at the start of the conference. For example, the patient's television screen will show only the intended consultant who may say, "Mrs. Remote and Dr. Distant, also joining me here is Dr. Jones, another orthopedic surgeon. He's sitting off-camera now, but I might ask for his opinion on your diagnosis and care."

Failure to notify the patient of a another consultant viewing the session does not violate the consent but is contrary to the implicit understanding that others in the studios are indeed disinterested.

Similarly, the consultant must know if there are persons at the patient's video-studio who could inhibit truthful answering of the questions. Twice, our physicians have learned after a VTC that patient's family members were off-camera in the distant studio, leading to concerns that perhaps some questions, eg, the sexual history, might not have been answered truthfully because of the family's presence.

If the physical examination requires partial disrobing, it comforts the patient to have an off-camera changing area, gowns, and some privacy screens in the camera field.

Informed Consent

To embody the principles discussed, we developed guidelines to use in counseling patients before their VTCs. Furthermore, we prepared a written Statement of Understanding for the counseling session and to serve as its record (Fig 1).

Conclusion

We strive to establish a relationship between the patient and the video-consultant that closely resembles the traditional patient-physician role. Sensitivity to issues of privacy and confidentiality—and full disclosure of the inherent difficulties—enables patients to feel more comfortable with their VTC and avoids unpleasant moments and depersonalized care. We hope it enhances the effectiveness of telemedicine and increases confidence in it on the part of the patients as well as that of both the consulting and attending physicians.

Our treatise is limited to few of the many ethical concerns of telemedicine. We encourage further endeavors in this field.

The opinions and assertions contained in this article are those of the authors and are not to be construed as those of the Department of Defense.

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The Advanced Clinical Information System: Physician-Focused

Daniel Davis MD*

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The U.S. health care system is being forced to change because of intense demands for better quality, decreased cost, and better service. These demands are driving the implementation of health-oriented computer technologies that will fundamentally change the practice of medicine. These technologies will enable physicians to find new opportunities to improve quality and reduce cost.

Seventy-five percent of health care costs are generated by physician decisions and half of all health care dollars are spent in the hospital.¹ Errors in the management of hospitalized patients occur frequently. Maki and others reported a 35% error rate in the choice of empiric antibiotics.² Castle et al noted a similar error rate in antibiotic use at a university hospital.³ An advanced computerized clinical information system with physician-order entry can reduce errors and improve the quality of patient care.

This paper describes the rationale for physician use of a computerized clinical information system and our initial efforts at The Queen's Medical Center to select and design a physician-focused order-entry and results-reporting system.

Major improvement in the quality of medical care will occur when physicians use computerized decision-support tools as part of their day-to-day patient care. Decision-support will be most effective if applied at the time the physician analyzes patient data and then orders diagnostic tests and therapies. Order-entry and results-reporting (OE/RR) is the term used for the computerized process of reporting patient test results, for the ordering by computer of diagnostic and therapeutic measures, and for a system of on-line medical knowledge designed to improve clinical decision making.

OE/RR is the cornerstone of an advanced clinical information system (ACIS) that physicians can incorporate into their daily practice. In the near future, physicians, nurses and other health-care providers at The Queen's Medical Center will begin using ACIS and OE/RR in their day-to-day care of patients. The advanced clinical information system will become as important to the good clinician as the stethoscope.

Rationale for Physician Order Entry

The rationale for direct physician use of OE/RR is that the best opportunity to improve patient care occurs when effective decision-support tools are placed in the hands of physicians. Specific reasons for direct use by physicians of ACIS are summarized in Table 1.

The goals of ACIS are to improve clinical care through improved decision making and to improve the efficiency of the physician's hospital practice through automation of time-consuming activities. The purpose of ACIS is not to automate patient care for the sake of automation, but rather to add value to the health care process by improving quality and efficiency.

Quality-improvement experts use a matrix (Table 2) to empha-

size the relationship between making the right decisions—that is, doing the right thing—and performing the work correctly—or, doing the thing right. The best opportunity for improving medical care—doing the right thing right—is to enable the physician to make the best clinical decision at the time the decision is being made. This enabling process requires accurate, timely and complete patient-specific data and extensive support for the decision, neither of which is possible without modern information technologies. Old methods of managing information, such as the paper chart, are inadequate in today's demanding health care environment. Medical charts on paper are often inaccessible, illegible or incomplete.

Tufo and Spiedel noted that in a traditional paper medical-record system, physicians were lacking important clinical information in up to 20% of patients' charts.⁴ Clinicians are then forced either to operate with incomplete information, guess about clinical data, or order duplicate tests. The accuracy of handwritten records has been questioned. Hsia reported that 20% of dis-

TABLE 1: Reasons for Physicians Order Entry and Results Recording.

- Manual order entry is unefficient and error prone.
- OE/RR can improve the quality of patient care.
- OE/RR can improve efficiency of care and decrease costs.
- OE/RR can improve communication among care givers.
- Access to clinical information can be increased while security and confidentiality.

TABLE 2: The Quality Matrix

Do the right thing right	Do the wrong thing right
Do the right thing wrong	Do the wrong thing wrong

TABLE 3: Tabular Form of Bayes' Rule.

A	B	C	D	E
Disease State	Pre-test Probability	Test Characteristics	Column B x C	Post-test Probability D / sum
present	.85	(sensitivity) .15	.13	.67
absent	.15	(1-spec) .41	.06	
Sum =			.189	

TABLE 4: Physicians Defined Critical Success Factors for OE/RR:

- Ease of use.
- Availability of work stations.
- Fast response time.
- Efficiency and time savings.
- Clinically valuable information.
- Security
- Minimal down time

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charge DRG codes were incorrect.⁵ Even when information about the patient is accessible and correct, the physician's decisions can be improved using the computer as support for making decisions.

Pestotnik et al noted that a computerized, therapeutic, antibiotic alert system identified 420 instances of inappropriate antibiotic therapy in 1,632 patients. Physicians were previously unaware of relevant susceptibility-testing in 49% of these alerts. Physicians apparently responded to automated alerts by changing antibiotics in 30% of such instances.⁶

Tierney reported that use of a computerized order-entry system for physicians significantly lowered charges to patients and also lowered hospital costs; the projected savings were \$3 million annu-

ally.⁷

ACIS should decrease the incidence of common medical errors. Consider a case in which the physician "does the right thing" by deciding to heparinize a patient with pulmonary embolism, but who "does it wrong" by failing to give an adequate loading dose of heparin. Improper performance of the right task resulted in avoidable risk to the insufficiently anticoagulated patient. Failure to achieve adequate anticoagulation within 24 hours of heparinizing patients is a common physician error. ACIS should decrease such errors by prompting the physician with an appropriate method of administering heparin at the time it is ordered.

Another example illustrates how ACIS might prevent a physician from "doing the wrong thing right": The physician correctly diagnosed mild enterocolitis due to *Clostridium difficile* and ordered oral Vancomycin in a proper dose. However, by not realizing that oral metronidazole is almost as effective as Vancomycin but costs substantially less, the physician missed an opportunity to make a better decision.⁸ Doing the wrong thing, even artfully, can be costly and harmful. Such decision-making errors can be decreased by computerized clinical information systems. Gardner et al reported a reduction in erroneous orders for antibiotics because of a computerized therapeutic antibiotic-monitoring program.⁹

Another example of clinical decision-support by ACIS is the provision of a tabular form of Bayes' rule for use in the analysis of tests analysis (Table 3). Such support might help prevent a physician from "doing the wrong thing". For example, a physician strongly suspected pulmonary embolism but the V/Q scan was read as low-probability for pulmonary embolism. The physician erroneously assumed that pulmonary embolism was not present. However, using a simple tabular form of Bayes' rule, data from the PIOPED study¹⁰, and the physician's estimate of pre-test probability, ACIS could have calculated the post-test probability of pulmonary embolism and communicated this probability to the physician, who then might have considered further testing or using anticoagulation empirically. QED, direct order-entry by the physician, based on ACIS would have improved the quality of care for this patient.

Barriers to Physician Order Entry

There are potential barriers to successful order entry by physicians.^{11,12} Physician-generated barriers include:

- The ABDF syndrome—"If it ain't broke, don't fix it";
- The "I'm in charge" syndrome;
- The fallacy that computers are illiterate;
- Computer-phobia and computer-mania.

The first barrier is the ABDF syndrome—"If it ain't broke, don't fix it". The U.S. does not have the best health care in the world; rather, the U.S. has the best tertiary care in the world for some.

Recently in our hospital the care of a critically ill and dying elderly patient cost almost \$500,000; at the same time, a young single mother developed *status asthmaticus* and was hospitalized because she had been unable to obtain a \$10 medication. Rational prioritization of the need for medical care demands high quality information regarding the clinical determinants of costs and outcomes. This clinical information will be obtainable and affordable only through the use of advanced clinical information systems. Through the direct use of ACIS and OE/RR, physicians will be able to contribute to the development of data on outcomes and the use of ACIS as a tool to improve quality.

A second medical staff barrier is the "I'm in charge syndrome" in which physicians declare that others are responsible for both inefficiency and high cost in health care, and that others should change their tactics in order to fix the system. Previously cited examples of medical decision-making errors clearly indicate the importance of the role of the medical staff in improving the quality of care. Quality is everybody's business. If physicians, nurses, ancillaries and administrators are not working together as a

(Continued) ➤

TABLE 5: Sources of Efficiency in ACIS:
• All clinical data should be available at a single geographic point.
• All clinical data should be made available to the clinician as soon as it is processed by the ancillary service.
• Clinical data should be available at locations other than the patient's floor.
• Clinical data should be available to remote sites.
• Phone time should be decreased.
• Order sets should speed order entry and promote standardization.
• Simple decision support will promote the choice of formulary products and eliminate phone calls to clinicians from pharmacists.

TABLE 6: Clinical Data Elements for ACIS:
• Demographic data.
• Historical data- previous surgeries, major medical diagnoses, family history, social history.
• Allergies.
• Problem lists.
• Discharge diagnosis.
• Current medications.
• Laboratory data—chemistry, hematology, micro, etc.
• Imaging data—imaging reports and images.
• Path reports.
• Cardiology results—EKG, ambulatory EKG, echocardiogram, cath reports, etc.
• Collaborative care plans.
• Code status and advanced directives.

TABLE 7: Steps in OE/RR Development at QMC:
• Alignment of OE/RR goals with institutional strategy.
• Defining the current environment of manual order entry.
• "Best of Breed" site visits.
• Extensive definition of user functional requirements.
• Detailed definition of user functional requirements.
• Requesting proposals from vendors.
• RFP analysis and selection of two finalist vendors.
• Site visits for the two finalists.
• Demonstrations by the finalists for QMC staff.
• Selection of a final vendor.
• Implementation.
• Ongoing CQI.

TABLE 8: Future ACIS Challenges:
• Automated discharge summaries.
• Clinical expert systems.
• Outpatient prescription writing.
• Resident procedure tracking systems.
• Resident sign out process.
• Complete long-term computer patient record.
• Community wide clinical data base.
• Telemedicine.

team to implement the ACIS, the risk of things going wrong is high.¹³

The argument against direct physician use of OE/RR and ACIS is that physicians should continue to write orders by hand because handwritten orders have worked in the past, are convenient for the physician and don't require physicians to change their ways. However, there are several problems with handwritten orders:

- Handwritten orders are all too often illegible.
- Clerks can misinterpret medical orders.
- Handwritten orders can be lost.
- Handwritten orders take too much time to complete.
- Physicians make errors in writing orders.

Illegible orders can lead to harmful misinterpretations and represent a legal liability. Bates et al reported that 28% of drug-ordering errors were generated by clerk, nurse, or ancillary personnel.¹⁴ Physician errors accounted for 72% of adverse drug incidents. In addition, such orders take too much time to write and to be interpreted; it was estimated that a typical medication order takes more than 4 hours to process.¹⁵ A study of stat intravenous antibiotic orders revealed that in such an order-entry system, 20% of stat intravenous antibiotics were not administered within the next 4 hours in the cases of suspected sepsis.¹⁶

Information-service (IS) personnel can generate barriers to physician order-entry by developing a sense of ownership of ACIS and by viewing ACIS as primarily an information technology rather than as a clinical tool. Failure of IS planners to include physicians early in the selection and design of clinical information systems is a common error that might stem from a sense of ownership of ACIS.¹⁷

The hospital administration might erect barriers to physician order-entry, which could be founded on the mistaken beliefs that:

- Physician involvement in ACIS is too expensive;
- Physician needs are incompatible with hospital needs;
- Physicians are too difficult to work with.

Bria describes reasons why an administrator might think that physician involvement in ACIS is unaffordable.¹⁸ One is that physicians might demand more remuneration for extra time and effort in using ACIS as a clinical tool. A second reason is that the administration might not trust the medical staff to work in the best interest of the hospital. The idea that physicians are difficult to work with is based on the observation that physicians often have unalterable opinions and are demanding with regard to quality-of care-issues.

What Physicians Should Do

Our physician-user groups and physicians from other hospitals have defined several critical factors for ACIS and OE/RR to be successful (Table 4).

Ease of use was the most important interface factor. Physicians asked for a windows-type, graphical-user interface: A pointing device such as a mouse, track ball, or light pen, and they also asked for on-line help.

The availability of workstations, fast response time and minimal downtime were defined as critical requirements for the system. Clinicians perceive downtime as any time that the system is unavailable for their use, regardless of the cause. If workstations are not available because they are placed in the wrong locations, or are too few in number, or do not function properly, physicians will view this as downtime.

We discovered a variety of approaches to the issue of availability during our site visits. These approaches include placing one workstation in the hall for every 4 beds in a functional unit called a pod.¹⁹ Advantages of the pod arrangement are decreased cost of hardware and less temptation by patients and families to play with the computer in the patient's room.

The pod configuration has several disadvantages however. Both doctors and nurses wait for the same workstation in the pod. When one care-giver is called away from the workstation for an emergency or a phone call, another person might begin working at the same

workstation, not realizing that he or she was logging in on the wrong patient or is logged on to the computer with another's identification. When the pod's workstation goes down, access to a workstation in another pod could be difficult.

Other institutions have placed multiple workstations at the nurses' station, typically one workstation for 4 acute beds. Some have placed a workstation in each patients' room or just outside the patient's door.²⁰ LDS Hospital in Salt Lake City, Utah, a 550-bed tertiary care hospital, uses 1,200 workstations, one in every patients' room.

Some institutions are experimenting with portable wireless terminals in the form of small notebook computers, pen-top computers, palm-top computers, and personal digital assistants such as the Apple Newton.^{21,22,23} At the March 1993 Healthcare Information and Management Systems Society meeting, 13% of surveyed institutions indicated that they had for the most part implemented a wireless, local-area network.²⁴

Physicians identified fast-system response as a critical factor for success. This requires the workstation screen to respond to user-input in less than one second, so called "sub-second response time". Sub-second response time might be difficult to achieve if the clinician's workstation must frequently generate access to a clinical data base or a behind-the-scenes decision-support system. To achieve sub-second response time in a complex network tied in to the lab, imaging and pathology computer systems, great demands are placed on network architecture and software interfaces. Each gateway, router, and bridge among networks adds a small increment of time to the data-access process, the total of which can cause a response time of several seconds in a complex or poorly designed ACIS. Thus, system architecture plays an important role in satisfying the physicians' functional demands.

Physicians also require that ACIS improve the efficiency of their work process. Time is money to clinicians, regardless of the payment system in which they work. Physicians identified several sources of efficiency that they expect from ACIS (Table 5).

One aspect of efficiency is having all relevant patient data available at one workstation so the clinician can avoid searching multiple locations to obtain clinical data. In our current paper medical-record system, the clinician often must go to one location for the chart, to another location for current labs, to another site to obtain vital signs that have not yet been recorded, and still elsewhere to locate the place where the administration of medications have been recorded. Often one of these key sources of data cannot be located.

Turn-around time for laboratory results can be decreased as a result of increased efficiency of computer order-processing. The clinician should have all lab results made available through OE/RR as soon as they are obtained by the laboratory, thus eliminating most telephone calls to obtain these results.

Another item of efficiency can come from being able to have access to clinical information from sites other than the patient's location. Thus, better and faster clinical decisions can be made from remote places within the hospital and from locations outside the hospital such as the physician's office and home.

Personal order-sets will promote efficiency by allowing customization of a physician's orders for frequently repeated procedures. Physicians should be able to customize their own orders, screens and user-areas without approval or help from IS. Department order-sets will promote adherence to more effective and efficient standards of care. The OE/RR should promote an easy method for the physician to automatically document the causes and medical necessity of variations in care and thus reduce unwanted calls from utilization reviewers and managed-care workers.

OE/RR will promote large increases in efficiency through the use of decision-support by physicians during order-entry. For example, formulary contents with default dosages should be immediately available, thereby eliminating the need to locate a drug reference book, which often is not available or is out of date. The antibiotic alert programs and Bayesian analy-

sis described above are examples of more sophisticated decision-support.

Another critical success-factor defined by our physicians was that the information contained in ACIS must be clinically valuable. Clinical value comes from having as much of the relevant clinical data as possible on-line. Examples of clinically relevant data that the clinicians expect to use in ACIS are listed in Table 6. Examples of value added to the clinical process are ordering guidelines, clinical alerts, cost information, medication-administration data, and knowledge-base information.

Physicians perceive ordering guidelines from OE/RR to be of value. For example, unnecessary duplicate orders and tests can be detected quickly, such as the concurrent prescription of Lasix by one physician and furosemide by another. Alerting the ordering physician to potential drug-interactions is another value added by the system. Drug-allergy interactions and drug-lab test interactions are common unwanted events that can be decreased by ACIS.

Another critical success-factor defined by our physicians is in ensuring the security of patient information, referring to data integrity and patient confidentiality.

Integrity of data refers to maintaining the validity of the information within ACIS. This includes such issues as the frequency, method, and reliability of backup data, whether duplicate data bases are to be maintained, and which data base is the official record.

Confidentiality refers to the process by which privacy of patient data is maintained. Confidentiality issues for ACIS are basically the same as the confidentiality issues for the traditional paper chart, for which the medical staff currently has policy. Remote access through a modem raises special problems of confidentiality. Control of a legally binding electronic signature for clinicians is related to the data integrity issue.

Previous Failures of Clinical Information Systems

Given the volume of clinical information, the large number of users of this information, the movement of patients among multiple services within and between health care institutions, and the complexity of the information infrastructure, it is not surprising that some clinical information systems have been plagued with problems. It is essential for those planning to install ACIS to analyze the failures and problems of other systems.

Interviews with physicians at several hospitals, clinics, vertically integrated health care organizations, and a review of the literature revealed failures common to several advanced clinical information systems. The most common problem is the failure to involve the clinical staff in the selection and design of the system from the beginning. Another common problem is the failure to include important clinical constituents, such as resident physicians, in the design and implementation process. Most institutions report that only a small fraction, typically 15% to 30%, of their physicians use the clinical information systems. In contrast, some hospitals report very high usage among physicians. At El Camino Hospital, a medium-sized nonteaching hospital in San Jose, California, almost all orders are entered by the physician directly into the OE/RR computer system. El Camino attributes their remarkable efficiency to the clinical information system.²⁵

The QMC Response-Vision, Strategy, Structure, Staff

The QMC vision for the Order-Entry/Result-Reporting project is to create an efficient and effective computerized process which will enable QMC health care providers to manage orders and receive results efficiently in order to achieve the best possible patient care and to promote continuous improvement of quality.

Our process for developing the OE/RR project is composed of discrete steps (Table 7). These steps focus on analysis of the current manual order-entry environment, definition of user needs, determination of IS requirements, and alignment of the OE/RR project goals with institutional strategy.

The OE/RR Steering Committee is composed of members from major clinical and ancillary staffs and from hospital administration. The OE/RR Project Team consists of representatives from the medical staff, nursing staff, ancillary departments, man-

agement, engineering and IS. User groups are organized to represent user constituencies. Personal invitations were extended to 140 active medical staff members to participate in the Physician User Groups (PUGs). About 70 physicians have been actively involved in the OE/RR process. Similar user groups have been organized among the nursing staff, ancillary staffs, and among the nonclinical departments.

It is anticipated that the OE/RR organizational structure will resemble the structure of other institutions that have implemented advanced clinical information systems.²⁶ A multidisciplinary Clinical Informatics Committee will be needed to set policy for ACIS and OE/RR and develop quality clinical initiatives for the medical center. The Clinical Informatics Committee should report regularly to the Medical Executive Committee and the administration. Implementation of clinical initiatives and the initial system design will require a Physicians Clinical Informatics Group (PCIG), which will consist of 6 to 8 physicians with special interest in the application of OE/RR for solving clinical problems. The PCIG members will serve on the Clinical Informatics Committee and they will be responsible for the day-to-day screen development and for ensuring rapid response on the part of the OE/RR Project Team to clinical needs. The PCIG will collaborate with the Nursing Clinical Informatics Group (NCIG), ancillary services, IS, and the OE/RR vendor.

A larger number of physicians will be recruited to participate informally as "friends of ACIS" who will serve as testers of additions and modifications of the ACIS. The physician, nursing and ancillary user groups will function as educational and advisory bodies to the PCIG and NCIG.

Future Challenges for Advanced Clinical Information Systems

Future challenges to the QMC ACIS will depend on the extent of health care reform and on how rapidly clinicians learn to use OE/RR. Possible future challenges for clinical information systems are listed in Table 8.

Advanced clinical information systems and direct physician order-entry are powerful clinical tools that will dramatically change clinical medicine. Physicians should lead the application of these technologies to day-to-day clinical practice in order to improve the quality and efficiency of patient care. Through careful planning, learning from others, and involvement of clinicians from the earliest stage, QMC will use these powerful new clinical tools to meet the demands of our rapidly changing health care environment.

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Computer-Assisted Search of Medical Literature

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Computers now offer physicians a wide range of time-saving and cost-effective means of user-friendly access to medical literature. This article describes different methods of using the computer to find information on a subject, focusing on end-user services that provide access to MEDLINE. The different systems available and their respective advantages and disadvantages are described. Use of electronic bulletin boards, Internet and online publishing in medicine also are addressed.

Physicians today have an ever-increasing array of methods available for access to medical literature. They can search libraries' on-line catalogs to see what books are available on a particular topic or they can search bibliographic data bases to retrieve references and abstracts from journal articles on a desired subject or by a particular author. Searching the journal literature can be done through the services of a librarian or by physicians themselves through a variety of direct dial and CD-ROM services. In the last few years physicians have even been able to search full-text data bases that contain the entire text of selected journals and books.

What is Computer-Assisted Search?

Computer-assisted searching is simply using the computer to find articles or information. Until the early 1970s, searching of the literature was done manually, using card catalogs and the printed indices to journal literature, such as *Index Medicus* or *Biological Abstracts*. With the advent of electronic publishing and the development of MEDLARS (Medical Literature Analysis and Retrieval System) by the National Library of Medicine, the ability to search the electronic information being used to print the indices was developed and enhanced. The electronic version of a print index that can be stored and retrieved on a computer is known as a bibliographic data base because of the bibliographic nature of the material retrieved. Sometimes these data bases have information available that the print index doesn't, such as authors' abstracts or summaries of the articles. Other data bases, known as full-text data bases, contain the actual information printed in textbooks and journals. Depending on the software developed to search the data base, the searcher uses a variety of techniques and commands to look for the desired information.

Why Do It?

There are many advantages to searching the literature with a computer. One major advantage is that the data bases are much more current than the comparable print index. The print *Index Medicus* lags several months behind its on-line counterpart, MEDLINE. Another major advantage is the ability to search for a combination of words or topics that can be looked up only one at a time in *Index Medicus*. For example, if the researcher is interested in how exercise affects adolescent asthmatics, the on-line retrieval can be restricted to articles that discuss the 3 subjects of exercise, asthma and adolescence and can

restrict the references to certain years or publication types.

Computerized searching of the literature also allows the searcher to use the advantages of an on-line subject thesaurus better. The National Library of Medicine assigns each article 5 to 20 Medical Subject Headings, known as MeSH headings, to describe the subject content and article design. These headings group articles on similar topics under one heading. For example, all articles on heart attacks or MIs will have the subject heading Myocardial Infarction assigned to them. All MeSH headings are arranged in a hierarchy that indicates broader and narrower terms of a topic known as a tree. Under antibiotics the searcher would find a list of various antibiotics including penicillin and streptomycin as well as a multitude of others. Using the print index, each type of antibiotic needs to be searched separately to do a comprehensive search. The on-line version allows for the search of the main subject and all the narrower subheadings under that subject all at the same time. It is critical for a searcher to use subject headings to achieve the best results. MeSH is also used for the subject headings assigned to books in a medical library collection.

Computer searchers also can search for articles containing certain words or combinations of words, which is called keyword searching. Keywords should not be too general; words such as "disease" are too broad to have much meaning. It is more helpful to search for words that uniquely describe the topic. Keyword searching is especially useful to search for articles on topics too narrow or too new to have a specific assigned subject heading.

Computer searching has several other advantages, including being able to search many years of the data base simultaneously. Searchers can stay abreast of the latest information by saving a literature search on a specific topic and thereafter running it at regular intervals to retrieve the most recent information on that subject. They can also search and print the abstracts of the articles that are available for a large portion of the data bases.

MEDLINE

MEDLARS is the computerized system of data bases and data banks offered by the National Library of Medicine (NLM). The entire system contains more than 13 million bibliographic and factual references in about 30 on-line data bases, including TOXLINE, CANCERLINE, PDQ, HEALTH, and MEDLINE. A comprehensive list and description of available data bases is available from NLM.¹

Of the data bases produced by the NLM, MEDLINE is the world's leading bibliographic data base for medical information. It contains the information found in the print publications *Index Medicus*, *International Nursing Index*, and *Index to Dental Literature* and provides access to the information on medicine, nursing, pharmacology, dentistry, allied health sciences and health care delivery; MEDLINE contains more than 6 million journal references, indexing over 3,500 journals from 1966 to the present.³ Abstracts have been available since 1975 for approximately 65% of the references. MEDLINE uses the medical subject headings known as MeSH. To search accurately for a specific topic, the searcher must know the MeSH term for that topic. Most of the end-user systems have the MeSH headings on-line. Because MEDLINE is the primary data base used to provide access to the medical literature, this article will focus on services that use MEDLINE. Most of the services offering MEDLINE offer access to other data bases as well.

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Develop A Computerized Medical Library

Today, all academic medical libraries and most hospital libraries provide computerized literature searches for their clientele. A physician should contact the medical library at the institution with which he or she is affiliated for details about the type and cost of services provided, whether they will accept requests for searches by telephone, and whether they will pull and photocopy articles retrieved. Most medical libraries will have many other computerized data bases available for searching in addition to MEDLINE. Before requesting a search, the requester should identify the purpose of the search, the key concepts or key words within the topic, and the synonyms for each concept, as well as consider any limitations such as the years covered, type of publication, language, or species. After obtaining the necessary information the librarian will then execute the search by dialing into the MEDLINE data base.

The advantage of having a librarian do the literature search is that the searcher utilizes a professional who is familiar with the data base, who understands the structure of the data base and can search it for maximum relevant retrieval. Physicians with limited time or inclination to learn to do their own searching find this a valuable service. Physicians who search infrequently also will find a librarian's services more cost-effective and satisfactory.

If You Do Your Own

An increasing number of physicians are discovering the advantages and the rewards of doing their own searching. The MEDLINE data base, and many others, is available for searching from many private companies and vendors that sell on-line access for end-users. There is a wide variation from company to company of the costs, data bases available, hours of availability, user-friendliness and the requisite hardware and software. At minimum, a researcher needs a microcomputer, a modem to allow the computer to communicate over phone lines, a communications software program, and an information vendor who will provide access to the data base and the search software necessary to search the data base. Several companies provide their own communications software when a user subscribes to their service. Expenses generally include communications costs, the data base-connect charge, a fee for every article displayed or printed, as well as an initial signup fee, annual fee and/or minimum monthly fee. Table 1 compares some of the features of the various services that provide access to MEDLINE and other health-related data bases, including their costs and the telephone number of the company to contact directly for further information. Most companies distribute demonstration diskettes that enable a user to compare and review the systems before subscribing to them. Some considerations before selecting a company should be the equipment required, hours of access, charges, ease of searching, availability of a manual or training, availability of a MeSH thesaurus, number or type of data bases offered, availability of a document delivery service, and any other special features of the data base.

The 2 services most appropriate for the novice or infrequent searcher are Grateful Med and PaperChase.³ Grateful Med is the on-line service offered by the NLM, providing software designed to simplify the process of searching the MEDLARS data bases. The user who formulates the search first, connects to the computer at NLM, runs the

search, disconnects, then prints or displays the results. It is relatively inexpensive and easy to learn and use.

An alternative search method is available for more experienced users. Grateful Med has an on-line document-ordering feature, LOANSOME DOC, to enable users to order copies from a medical library of articles for citations retrieved. PaperChase, developed by Beth Israel Hospital and designed by physicians, was the first user-friendly vendor for searching MEDLINE. PaperChase is available through CompuServe or directly from Beth Israel Hospital. This service also requires no special training.

More experienced searchers, or those desiring a more sophisticated service, might find BRS, NEXIS, or DIALOG more appropriate. BRS has the advantage of cost as well as providing access to the greatest number of medically oriented data bases, including many full-text book and journal data bases. Its Comprehensive Core Medical Library data base contains full-text articles from 80 major medical journals.

Direct on-line searching also is available to individuals affiliated with a university or other institution that has purchased and mounted the MEDLINE tape data for the use of their students, staff, or employees. The cost to do this is prohibitive for most institutions.

There are many advantages of doing your own on-line searching. One of the major advantages of personally searching the literature is that it can be searched from home or work, day or night. Another advantage is that the physician is able to incorporate his or her own medical knowledge into the search, sometimes resulting in more pertinent retrieval. Also, he or she can modify the search strategy immediately if the results are not satisfactory. Another advantage is that the searcher can download the results, transferring the references or information to his or her own computer's data base or word processor.

Although personally searching the literature is advantageous when only a few references or review articles are needed, for com-

(Continued) ►

Where can **YOU GO** this weekend?

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- ... **ocean kayak,**
- ... **visit ancient temples,**
- ... **shoot a round of golf**

... and still be back
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plex or comprehensive searches it is best to consult a librarian. Some disadvantages to direct on-line searching is that it is not always easy or cheap. The user needs to be familiar with the communications software, the search software and the command language. When a user pays according to time on-line or number of articles retrieved, he or she is less likely to experiment and try alternative search strategies.¹⁰

Searching MEDLINE on CD-ROM or Compact Disk

In 1986 the NLM released the magnetic tape of its MEDLINE data base to several companies to develop CD-ROM (compact disk read-only memory) counterparts of the data base. A compact disk is a 4.72-inch laser disk, the same shape and size as the CDs used for music. It is able to store the equivalent of 330,000 typewritten pages or 900 double-sided floppy diskettes on one disk.⁴ The result was that several variations of MEDLINE now are available on CD-ROM from 11 different companies, each using different search software. The NLM publishes a list of licensees who use its data bases to produce CD-ROM products.⁵ The hardware requirements are a relatively fast microcomputer, and a CD-ROM player with interface card and cable. Users wanting to search multiple years in one search will need a multiple CD-ROM player. Subscribers pay a fixed, annual subscription fee that entitles them to unlimited use.

CD-ROMS are very popular in medical libraries, largely due to the fixed cost, which promotes use, but also due to the ease of access, ease of use, and value as an instructional device. The fixed cost makes CD-ROM particularly cost-effective in institutional settings where there is a heavy demand for searching the literature. The data base also can be networked for an additional fee, making it available at multiple workstations. Many of the advantages of direct on-line searching also apply to CD-ROM searching; physicians are able to incorporate their own medical knowledge into the search, modify results immediately, and can download results for later transfer of the information to their computers.

There are several disadvantages to searching MEDLINE on CD-ROM. One disadvantage is that the relatively high annual subscription fee is prohibitive for most individuals. The CD-ROM data base also is not as current as the on-line version, largely due to time required to master the CD-ROMS and distribute them to subscribers. Another disadvantage is that MEDLINE requires a multiple CD-ROM player in order to search several years at once. The alternative is to load the disk manually for each year. A further drawback is that a subscription to MEDLINE on CD-ROM gives access only to that one data base.

The Future

There have been recent trends in other ways to gain access to the medical literature. One of most dramatic changes in the past 5 years has been the increasing use of electronic mail and bulletin boards to query colleagues on their opinions. Bulletin boards are on-line forums that allow participants to ask and answer questions. To have access to them users need a microcomputer, modem and specialized software. Some services, such as CompuServe, have access to a physician's bulletin board as well as bibliographic data bases such as MEDLINE. If a user is affiliated with a university access to it through its Internet or Bitnet networks might be available, which is usually less expensive than subscribing to a commercial service. Physicians might be interested in Black Bag Bulletin Board, to CompuServe's AMIA Medical Forum, to Fam-Med.⁶ Through the Internet a user also can have access to a variety of library catalogs and factual data bases. Just a few of the many interesting library catalogs a user can peruse are that of the Memorial Sloan-Kettering Cancer

Center, the Cornell University Medical College, the National Library of Medicine Online Catalog (the world's largest biomedical library), the National Institute of Health, New York University's Ehrman Medical and Waldmann Dental Libraries, and our own Hawaii Medical Library. Other sources of medical information on the Internet of interest to physicians include a variety of NLM publications, a collection of disability-related files, National Institute of Health articles and pamphlets and newsletters such as the *ALS (Amyotrophic Lateral Sclerosis) Digest* and the *Chronic Fatigue Syndrome Newsletter*. If you want to know more about the Internet and how to access the resources that are available, the book *The Whole Internet: User's Guide and Catalog* by Krol⁷ is valuable.

Another trend in medical literature is on-line publishing. OCLC published the first on-line medical journal, *Journal of Current Clinical Trials*⁸ which has received mixed reviews. Full-text journal sources generally delete graphs and charts that are available in their print version. *The Journal of Current Clinical Trials*, which has no print counterpart, includes charts, tables, and graphics as well as text. Included with the subscription fee is special software necessary to develop access to this journal. A few other full-text electronic sources on the Internet include the *Morbidity and Mortality Weekly Report (MMWR)*, *The Scientist*, the *AIDS Information Newsletter*, the *Family Medicine Digest*, and *Springer Journals Table of Contents Service*. Most of the services described in Table 1 offer a variety of full-text data bases where the complete text of articles is available for the searching. The *New England Journal of Medicine* and *JAMA* are 2 of the many journals available on-line for full-text searching. Access to the world's drug literature also is easily searched on-line.¹³

Although there are obvious benefits in using electronic sources to search the Internet and full-text data bases for medical information, there are important factors to consider. These sources generally require more computer literacy and a greater investment of time and money. Copyright issues are also still under consideration as to their being accessible.

Conclusion

There are a growing number of ways physicians can obtain access to the medical literature. A physician should be able to find a system that matches his or her needs and inclinations. Although personally searching with the computer can give a physician immediate, inexpensive and flexible access to the literature, it is not for everyone. The physician must select the computer and the information company that is most appropriate to his or her needs; the physician also must be willing to invest the time to learn the system if it is to be used to its maximum potential. We have attempted to present some of the different systems available with their advantages and disadvantages. More information on many of these systems is available from your medical librarian.¹⁴

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Computer Imaging: True or False

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Technologic advancements in the field of computer imaging are providing plastic surgeons with the ability to give patients a visual forecast of postsurgical outcome and serve as a platform for improved doctor-patient communication. This same technology allows the convenient and stable storage, cataloguing and rapid retrieval of massive numbers of photographs in minimal space. Along with these positive aspects, negative ones are becoming apparent. Poor prediction of outcomes by the physician, whether conscious or not, could result in patient dissatisfaction with what might be an optimal operative result. The hard copy evidence of the predicted outcome may then serve as evidence in our very unyielding legal system. Our inability to discern altered from unaltered photographs, negatives and slides presents our profession with ethical challenges in the presentation of data to our peers. Some partial solutions are discussed but the advent of this new technology calls us to a unique and absolute commitment to professional honesty.

Introduction

We are bombarded daily with the products of professional photography that have been digitized, altered and retouched to form striking images. Medical photography has long been the staple of record keeping and conveyance of techniques and results to our peers. As plastic surgeons, perhaps more than other medical specialties, we select and modify our procedures based on published and presented photographic records. This is natural for such a visual specialty. We have availed ourselves of the new technologies of photography and computer imaging for all of their positive aspects. We now realize there could be some drawbacks to what these technologies allow us.

The Technology

The rapid march of technology has revolutionized medical photography. We can presently photograph (or *image* a patient, in the new jargon meaning to photograph in such a way that a computer can understand the picture) with the resolution of the best quality cameras of old. Indeed if a negative or slide format is used, the resultant photograph can be used and scanned into a computer for digitization of the image. Both Figures 1 and 2 in this paper were produced in such a manner. They were scanned (meaning to read a photograph or document by a computer) with a high quality VHS camera. Much higher resolution can be afforded by scanning with a flatbed scanner of 1600 dpi (dots per inch) resolution or, even better, scanning negatives or slides into the computer by way of a film scanner (capable of 3072 x 2048 pixel resolution—equivalent to 2000 dpi or that afforded by high quality photographic film). The direct digital transfer of images into the computer can attain even higher resolutions when there is no analog media intervening. Even with the limited resolution of the

technique available to us, very little difference can be discerned between the original photograph and that generated by the computer, other than a slight, generalized *blurring* of the image. Current high resolution pictures stored by the Kodak™ system allow only 100 photographs per compact disc (CD); however, data compression allows much higher storage capabilities and current computer-imaging compression (with slightly less resolution) allows for 10,000 images to be stored on a gigabyte drive—the storage space equivalent to a CD. The output for the *hard copy* of the image—that which we can see—can be on any format depending on the type of black box that is affixed to the output end of the computer. Slides and negatives can be easily generated, and from them, classic photographs, or, if desired, photographs of equal resolution and stability can be generated directly onto special paper and a high-resolution, color photograph produced immediately without the need for photo processing or the storage of slides and negatives. Computer images are stable indefinitely and simple backup of files eliminates the possibility of loss. Storage of the backup files should be away from the computer and the office; many physicians store the backup files at home. This technology is decreasing in price daily and will soon be the standard manner of stable, safe and economical storage of images.

Computer imaging is somewhat different from the above outline of state-of-the-art medical photography. Computer imaging uses the above technology but then the image is altered. This can be likened to original writing and typing of documents that has since been revolutionized with the advent of word-processing technology. We now can change images as readily as we can change words. Modern software allows an almost limitless array of abilities in this area from simply changing silhouettes, backgrounds and textures to automatically erasing shadows and filling in the altered area with identical color and texture foreground when a change in contour has been made. The contour edge, similarly, is automatically matched to its adjacent edge yielding an imperceptibly altered outline. The ease of these procedures is truly phenomenal. Image changes are now almost instantaneous.

Positive Aspects

Perhaps most important, particularly in the field of plastic surgery, computer-imaging technology allows the ethical surgeon an easel as a platform for the examination and discussion of what is most desirable aesthetically. This can be expanded to other specialties by allowing a platform for the discussion of surgical procedures and medical events. We can exploit this technology to improve physician-patient communication and facilitate understanding by patients of their condition, medical and surgical interventions. This means of communication often serves to crystallize patients' wishes and is a way of outlining surgical possibilities in our field. Immediate images and alterations are possible to facilitate this.

The efficient storage and ready retrieval of images coupled with the ability to catalogue them and compile them under groupings other than by patient name or identification number allow us to critically look at surgical results as compared to predictions. This previously took many years of intensive and critical review of photographs of

(Continued) ►

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patients; now the process is abbreviated and streamlined and allows us to look at groups of similar patients quickly and easily to see if our procedures measure up to our expectations. The selective memory that we often possess regarding good and poor surgical outcomes in recalling the last 5 cases, or the best or the worst result, can be aided by such imaging. The subconscious bias in our care of patients may indeed be alleviated as we are confronted regularly and readily with the surgical results. We can then be able to predict outcomes more accurately as sequelae of our surgical actions and rely less on memory alone to determine future surgical procedures and techniques.

Additionally, this way will be used by many surgeons because of its convenience, stability, safety and efficiency. Lost photographs will be a thing of the past.

The ability to rely on an *in-house* system allows for greater retrieval of images as well as of hard-copy photographs. It not only saves a great deal of money following the initial investment, but makes available images for review pre-, intra- or post-operatively. The photographs can be cross-referenced in patients' charts; if the latter are digitized, the 2 can be readily integrated. The quality of the images can be regulated readily and the ability to digitally overlap images allows for exactly the same patient attitude, angulation and lighting in pre- and post-operative images—as well as in between patients—a perennial problem in medical photography.¹



Figure 1: Computer-generated image of a true post-operative result (*Left*) and a computer-generated image with no basis in truth (*Right*). The patient had a tertiary rhinoplasty and the projection of her nasal tip. Although it was the best achievable for her, it was suboptimal. She is very pleased with her operative result, as it is a great improvement over her condition pre-operatively; however, would she be as pleased if the image on the right had been predicted erroneously pre-operatively?

Negative Aspects

Dishonesty or at the very least poor prediction of operative outcome is the most overt of the bad aspects of computer-imaging technology. Misrepresentation of what can be done, delineating impossible surgical outcomes is obviously unprofessional and unethical (see Fig. 1). The use of computer imaging as a sales or marketing tool is mentioned only to be condemned. Flagrant misrepresentation to patients will only debase our profession.

Less obvious is the fact that patients could mistake facility with the computer for surgical expertise. The ability to alter images on a computer obviously is no indication of the ability to alter form or function in the operating room.

The hard copy of predicted surgical outcome given to patients could serve as a platform for lawsuits despite appropriate disclaimers. The fact that hard evidence of what was promised preoperatively does exist might help us, again, to analyze critically our procedures and methods.

Unfortunately, healing characteristics of individuals and unforeseen complications leading to subsequent poor or altered outcomes are predictable. In the present legal climate, a promised result, particularly

with detailed evidence to support it, will not be able to be upheld against a poor or altered outcome. More so, an overly optimistic prediction of surgical outcome, despite perhaps an optimal result for that patient may lead to dissatisfaction with what might otherwise be an acceptable outcome.

Some users of computer imaging do not give patients a hard copy of the predicted outcome. Whether this is in the patient's possession, or in his or her memory, we must be as honest as possible with both our patients and ourselves.

Minor negative aspects of this technology are its present cost. Sophisticated systems complete with software cost about \$25,000 to \$30,000. This cost must be absorbed by the office and will ultimately be passed on to our patients. Some practitioners charge for imaging although, in time, it will likely integrate into our practices. Costs decrease almost daily, particularly for the computer hardware.

Loss of data is easily circumvented by regular use of backup and the use of read-only formats. In the latter category are CDs that require special equipment to boot up. There are WORM (write once, read many) drives that can be used. Optical drives allow the ready and relatively inexpensive storage of large amounts of data and are often the preferred current day format of computer imagers.

Perhaps the most serious repercussion of this new technology is the reality that no

published or otherwise presented image need be based on fact. More than in any other discipline, plastic surgeons select and modify procedures based on published and presented photographic records. This is natural for such a visual specialty and it is also natural that we try to present our work in the best possible light; this occasionally leads to unintentional (or intentional) misrepresentation. Until recently such misrepresentation could be accomplished by such benign methods as altering the light source and the intensity of lighting, altering posture and position, altering appearance with makeup or varying hairstyles, and changing camera focus and focal length as well as distance to the subject. Fortunately, there are clues to these classic distortions making them evident to an astute critical analysis of the photographs.¹

Today this is no longer the case. We now have the ability to modify readily our results in every way imaginable (see Figs. 1 and 2). There is no requirement for an original photograph before and after surgery; any image is alterable. When we convert to images that are computer-generated for both pre- and post-operative images, we lose our fixed point of reference. This loss does not allow any way of ascertaining the



Figure 2: (Above Left) Unaltered, pre-operative photograph of the patient; notice the right upper lid ptosis. (Above, Right) The original, unaltered, post-operative photograph of the same patient. Ptosis correction, upper lid blepharoplasty and lower lid shortening procedure was performed. (Below, Left) The computer-generated photograph of proposed operative correction. Note that this photograph is almost identical to the true post-operative photograph. (Below, Right) Another computer-generated photograph of the patient taken from the true post-operative photograph with correction of the mild ectropion. This photograph has no basis in truth.

authenticity of the photographs or images of the patients. Indeed, at the present time, there is no guarantee of authenticity of any before or after surgical photograph presented by any media.

There may be ways of discerning digitally altered images by inconsistent shadows or minute inconsistencies in outline but, practically speaking, with the resolution offered by the software available today, such detection is impossible. We have already mentioned that submission of negatives and slides is no help in ascertaining authenticity since they can be computer-generated readily. The user-unalterable nature of CD technology may be of some help in that images could be submitted to a licensed and bonded agent for transfer to these disks. There is still the lag between hard disk, diskette or tape storage and CD transfer where images are imminently alterable by the user. Developers of computer imaging software have anticipated the possible problems with authenticity and one company (Mirror Image Technology, Lynnwood, Wash.) has incorporated a pixel counter into its software. This prints an original symbol on an image read into the computer and any alteration of it leads to a different pixel count and subsequent erasure of the symbol. This is a thoughtful step on the part of the imaging industry; however, it is likely to be easy to alter the computer code generating the seal. It will furthermore prove useless unless the seal is required on all photographs submitted for publication and that would be possible only if all authors have identical software and imaging systems, an unlikely prospect.

Conclusion

Digitized medical photography and computer-imaging have many positive and negative aspects associated with their use. The advent of this new technology calls us to make a unique and absolute commitment to professional honesty on many levels. If we fail to rise to this high calling, we will cease to be led by those with skill, creativity, insight and experience into using the best and most effective procedures. Instead, we will find ourselves following those with the greatest computer proficiency and the lowest levels of professional ethics. Affidavits regarding authenticity and oaths as to photographic honesty offer assurance, but unless we are absolute in our commitment to truth, our profession will be up for grabs.

Acknowledgments

The authors thank Dr. Norm Goldstein for the solicitation of this article and to Ray Lindford of Mirror Image Technology (Lynnwood, Wash.) for the computer-generated images presented, as well as for useful technical discussion.

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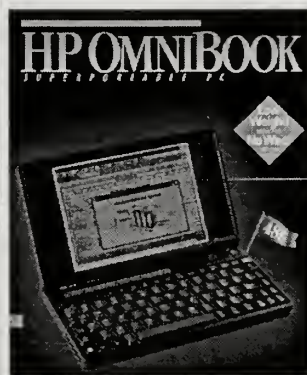
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Emergency Room Psychiatric Consultation Data Base

Harry T.G. Chingon MD, BS*

The University of Hawaii Affiliated Hospitals Residency Program supports The Queen's Medical Center Emergency Room (ER) by providing a resident physician for psychiatric consultation. In an effort to improve patient care, the residents are working with the hospital to computerize the psychiatric consult service to ease the problems of limited space in the ER for psychiatric examinations. Limited psychiatric office space, and time wasted walking back and forth from the nursing station are handicaps. This article will describe the current system and compare it with the system being developed. The ultimate goal is to make consultations more efficient by creating a data base of known patients, and by increasing the speed of evaluating and processing patients, thus reducing the amount of time a patient spends in the ER.

Psychiatric residents are asked to evaluate 9 to 18 patients per 24 hours; these take an average of 60 minutes each, while during the same period the resident has to provide psychiatric emergency consultation support to a 500-bed general hospital, ie, while assessing and treating patients in the ER, a resident regularly must see patients on all medical and surgical wards.

Within the ER there are only 3 psychiatric examining rooms available for patients, and these are easily filled when 3 or 4 patients arrive within 2 to 3 hour, which is a common occurrence. The limited space also is made more critical when intoxicated patients occupy one or more of the psychiatry rooms while they await sobriety. Given this problem of examination room availability, reducing the time for the assessment of previous psychiatric histories is a logical solution for reducing the time patients need to spend in the ER.

The official psychiatric resident emergency room consultations are handwritten on a 3-part carbonless form. For at least the past 5 years residents have been filing their copy of the reports as a reference for when patients return; they also are useful for research projects. This has amounted to 2 large filing cabinets taking up 25% of the psychiatry residents' office spaces. Often, the staff who previously filed the reports are no longer available to search the file. The location of the ER psychiatric residents' office is about 30 feet from the nursing station, which needs to be traversed many times during the evaluation of a single patient, to: (1) Pick up the ER clipboard, (2) pick up old charts, (3) order labs or medications, (4) pick up lab results and to, (5) drop off admission or discharge orders. Unfortunately, time is wasted walking back and forth between the office and the nurses' station.

A computerized system addresses most of the problems with forms, filing, environment, and logistics by instantly optimizing access to pertinent data bases involved in patient care.

To identify our needs a committee of interested residents met periodically and developed specifications on the data that needed to be collected for the evaluation of a patient. A primary concern was that it be very user-friendly since all residents are not computer-literate or cannot type as fast as they can write. To make

the computer worth the effort for residents, there needs to be a perceptible improvement in order to make learning a new system justifiable. As such, an icon-based (windows type) environment with a mouse is likely to be the most user-friendly. The Apple/Macintosh format was a popular alternative that was requested by some residents; however, The Queen's Medical Center standard is IBM which led the committee to agree unanimously on the window's format.

The next step was to choose the right computer; we knew we wanted at least a 486 CPU, and the faster the better. It would not go over well with our users if, to save time, they would be forced to use a computer, and then find they had to wait for the computer. Fortunately, once again we found QMC's existing system to be compatible with what we wanted.

As for hard-disk capacity, we didn't know how much would be required. The questionable short-cut taken was to ask a medical software package manufacturer how much hard disk space their package required to handle 5 years of patients' records at an average of 10 a day—questionable in that the amount of data saved by our current system may have been completely irrelevant. This was unintentional, as at first we examined 3 medical software packages (two IBM-based and one Mac-based) for the possibility of using one of them on our computer. Those packages were rejected by the new evaluator because they included too many unnecessary office procedures: Electronic billing, prescription writing, appointment scheduling. They were not task specific so as to make them easy to use by 35 residents and attendings. The software packages would not be flexible enough to incorporate Diagnostic Laboratory Service reports and QMC's Order Entry.

Additional clinical software that might be added in the future included a drug interaction warning system and an aid in diagnosing and treating psychiatric disorders.

Features that make the system easy to use are very important. With the use of icons and a mouse, the user should be able to move from one application to another rapidly and easily. Defaults and short-cuts so the user is directed to frequently used areas with a minimum of mouse/keyboard effort were priorities. The system should allow interruption of one activity, such as writing a report, to search the data base, then return to where the report left off. Working in an emergency room is often chaotic; therefore, the programs should save the files when the user has to leave the computer unattended, and then return to the users' place before he or she had to leave. Also for the purpose of medical record security, the computer should be able to request a password after being unattended for a specified length of time.

We have pointed out how a computer can help in several problem areas. The bulky file cabinets can be replaced by a hard-disk drive with tape or floppy disk backup which would eliminate the problem of hiring a file clerk. By using a laser printer, reports would always be legible. Laboratory reports would be available in the residents' office by direct transmission from the main hospital computer.

Difficult patients who are frequent visitors to the ER would have their patient care plans that are developed during morning reports instantly available for faster disposition, thus reducing the time spent in the ER. This would also help to reduce the problem

(Continued on page 354) ►

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All things being equal, you lose.

Your American Medical Association is loading up to challenge the Clinton administration's health plan. Specifically, we (that's us—the member docs, the AMA) have engaged a major Chicago law firm to explore the legal limits on various changes being considered. Attorneys consider that the U.S. Constitution puts tight constraints on how much the plan can limit doctor's fees and patient's access to care. The Sixth Amendment limits the unfair taking of property.

Technology is dominated by two types of people: Those who understand what they do not manage, and those who manage what they do not understand or *Fancy Gizmos don't work!*

In this contemporary world where biotechnology is greedily wagging the medical practice dog, catastrophes are bound to occur. The willingness of physicians to accept new devices, anticipating an evolving standard of care, plus the marketing pressure of manufacturers to sell the latest "advance" can result in iatrogenic horror stories, eg, the silicone breast implant episodes, and the synthetic visco-elastic glaucoma cases. Another outrageous story is the Vitek laminated teflon/proplast implant for temporomandibular joint syndrome.

When the device first arrived on the market, oral and maxillofacial surgeons enthusiastically began to use the implant because it successfully relieved pain. Now, 25,000 patients later, the implants are approaching 100% failure with bone erosion, jawbone collapse, constant pain, difficulty swallowing, inability to chew, and facial disfigurement. Some patients have become so depressed they considered suicide. Vitek is bankrupt and out of business and Dr. Homsy, inventor of the implant, is in Switzerland. "This is the worst disaster our specialty has ever faced," according to a Dallas oral surgeon. Therefore, the moral is: The promotional cliché *state of the art* deserves careful scrutiny before acceptance. Additionally, several events have revealed the FDA simply cannot be relied on in every instance.

Will all interested members please stand?

Instant fame. James Sehn MD was a comfortable, unassuming journeyman urologist who happened to be on call the morning of June 23, 1993. He was summoned to the hospital to care for a man whose spouse had amputated 2/3 of his penis and discarded it from her moving car into some roadside grass. The police recovered the missing portion, packed it in ice and brought it to the hospital where Dr. Sehn and a plastic surgeon spent 9 hours in reconstructive microsurgery. Result—vital organ. Dr. Sehn found the media waiting for him when he left the OR and has since become a celebrity with appearances on national TV, interviews by radio talk shows, and now the subject of foreign news magazine stories. Previously he claims he was ignored at cocktail parties, but now finds himself surrounded by people, almost always women, who want to hear all the details. No doubt Hollywood is planning a mini-series.

A lawyer is a learned person who rescues your estate from your enemies—and keeps it for himself.

On the national medical reform scene, the President has promised malpractice modifications as part of the package. However, the administration's just-revealed malpractice plan calls for disgruntled patients to engage in early settlements or to submit to a panel evaluation. Hawaii's malpractice data appear to support its MCCP method of resolving disputes, but apparently other states have had disappointing results. Even the President's home state of Arkansas gave up on the scheme. Lawyers claim the procedure causes delays and increases legal costs, since those proceeding to trial all must first clear the initial mediation hearing. Trust me, if lawyers don't like it, it is probably a good plan. Plaintiff's attorneys also are unanimous in opposition to California's proven effective MICRA statute.

Any bureaucracy reorganized to enhance efficiency is immediately indistinguishable from its predecessor.

While the American people are not sure what the problem is with our medical system, 78% agree with the admin-

istration that something must be done. However, there is no certainty as to precisely what is wrong. A *Wall St. Journal* poll showed that 42% think cost is the problem while 41% think the uninsured are the major problem. Seventy-five percent of those polled are satisfied with the quality of medical care and 69% are satisfied with access to care. Some troubling opinions about Hillary's proposals are that 38% believe small businesses will close, 58% think jobs will be lost, and 25% think their medical benefits will decrease. A fanciful 23% believe it will cut the federal deficit (66% disagree), and 63% believe it will help control health care costs. Eighty-four percent think there is so much waste in the system that costs can be reduced without affecting quality of health care. The indisputable fact is that government efficiency is an oxymoron: Bureaucracies enlarge and politicians know how to tax and spend. If you paid close attention to Messrs. Gore and Clinton planning to reinvent the government by reducing waste, you should have noted that *no* agencies were to be eliminated, but they would all be streamlined, eg, Congressional staffs. Yeah, right!

Chicken Little lives!

With a Fax alert, the American Society of Cataract and Refractive Surgery (our ever-alert nematode) has rushed a summary of the Billary health plan. Ranging from assumptions about optometric care to more Medicare cuts, the ASCRS report describes the near demise of fee for service, the dominance of managed-care plans, and increasing manipulation to encourage primary care away from specialty practice. Considering that influential Senator Moynihan (D) called the financial projections frankly absurd, it can be expected that when the smoke disappears and the mirrors have been removed, the plan will look much different.

Addenda

▲ You have taken yourself too seriously!

Aloha and keep the faith,

rts

Robert Flowers MD, is well-known to Hawaii physicians and residents. Having lived in Hawaii for more than 25 years, Flowers is an acknowledged world authority on periorbital aesthetic surgery and facial implants. Poetry by Flowers has appeared in many issues of the *Journal*, and we look forward to more. His associate, **Gregory Caputy MD** served his general surgery residency at Mayo Clinic and his plastic surgery in Halifax, Nova Scotia. Caputy and Flowers present a very honest review of computer imaging. This is an interesting paper that complements the "Virtual Reality" paper by Camara.

This issue wouldn't be complete without an article about library searches by computer, the most common use of computers in medicine today. Hawaii Medical Library has written a comprehensive "how-to" for physicians.

We'd like to extend an invitation to physicians to attend a Computer Exposition here in Hawaii at the Blaisdell Exhibition hall on January 26 and January 27, 1994. This is a must for both the abacus-using physician and physicians who now are using computers.

See you there and
Happy Computing!
Norman Goldstein MD
Special Issue Editor

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of limited space.

A fax/modem communications capability would speed up sending reports to mental health clinics after a patient gives written consent. In the future it also might allow access to other patient data bases. When the QMC order entry system is online in 1995, ER and admission orders will be entered conjointly.

Currently we have identified our needs and the specifications of our desired data base. An IBM model 56 computer with a 486 CPU, 8 megabytes of RAM and two 212-megabyte hard drives have been purchased. The psychiatry office has been wired to connect the QMC network. A new pushbutton combination lock has been placed on the door to prevent theft of the computer.

A problem we are still working on, however, involves standardization with other patient data bases within the Medical School. By the time this article is published the data base problems will be worked out, the software will be installed, and the users will be trained. When the system is installed, using the computer will probably be slower than the old system. As the users become familiar with the new system, processing evaluations will become faster, more efficient, and will produce better outcomes.

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WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.** Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin, the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t_{1/2}) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin. See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-24h} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitals, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a $\geq 50\%$ rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spiroclonolone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibuloacoustic Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses up to 50 mg/kg/day. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/m²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial palsy), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecostasia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination of in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

THE PRAVACHOL® DIRECTION
IN LIPID MANAGEMENT

Effective lipid management doesn't have to be tough



- Improves key lipids — significant reduction in LDL-C¹
- Excellent safety profile
- Easy for patients — once-daily dosing, well tolerated
- Usual dose: 20 mg once daily at bedtime, with or without food


PRAVACHOL®
pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate. Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.



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